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ORIGINAL ARTICLES.

THE PRESENCE AND IMPORTANCE OF YEASTLIKE FUNGI IN THE GASTROINTESTINAL TRACT IN PERNICIOUS ANEMIA, IN OTHER DISEASES AND IN NORMAL INDIVIDUALS.

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and

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For many years yeastlike fungi have been regarded as the etiologic factor in the clinical condition known as thrush. They were first recognized and studied by Langenbeck[1] in 1839. Since then they have been demonstrated many times in smear preparations and in sections of diseased tissue and have been isolated in pure culture from the lesions. Although most commonly seen in the buccal cavity, typical thrush membranes have been found at autopsy in the esophagus and stomach and occasionally even in the intestines.

Many investigators have studied the morphology, cultural characteristics and pathogenicity of the organisms isolated from thrush lesions. Fischer and Brebeck[2] were able to isolate two distinct varieties, the one characterized by the formation of ascospores, hence a true yeast, and the other by the absence of ascospores, hence an imperfect yeast. Castellani[3] claims that thrush may be caused by several different species of monilia and by other species belonging to different genera. A careful survey of the more recent

literature seems to indicate that most writers believe that thrush, at least in temperate zones, is caused, in the majority of instances, by infection with a specific yeastlike fungus, usually called *Monilia albicans*, although many other generic names have been given to the same organism. Five strains isolated by Fineman[4] were absolutely identical. They were readily differentiated from a miscellaneous group of "wild" yeasts, but could not be distinguished from 8 strains obtained from routine throat cultures of diphtheria suspects. It should be borne in mind that yeastlike organisms are frequently seen in stained smear preparations from normal and acutely infected throats, in fact, Brünstein[5] was able to recover yeastlike fungi from the oral mucous membrane in 40 per cent of normal individuals.

Langenbeck[1] was also the first to associate the yeastlike fungi with intestinal disorders. The patient on whom he carried out his studies on thrush in 1839 happened also to be suffering from typhoid fever; and, as he found similar organisms in the stools, he thought that they might also be the cause of the intestinal disease. For the next fifty or sixty years there are numerous references to isolated observations on the presence of these organisms in the intestinal tract. Accepting their presence as a well-known fact, Casagrandi,[6] in 1898, reported an attempt to determine whether or not any significance could be attached to such findings. He concluded that the yeastlike fungi are as frequent in the intestines of healthy children as in those with diarrhea, that the species in both instances vary from case to case, and that their presence has no relation to intestinal disease. Kohlbrugge,[7] in 1901, called attention to the large number of organisms, identical with the thrush fungus, *Monilia albicans*, in the feces, stomach contents and tongue scrapings from cases of sprue, and, although he acknowledged that similar fungi could be recovered in varying numbers from practically all stools from cases with diarrhea, he stated that they were never present in the stools in such enormous numbers, nor could they be recovered from tongue scrapings. These findings were corroborated by Le Dantec[8] and Bahr,[9] but denied by de Haan[10] and van der Scheer.[11] Castellani[12] has isolated several species of monilia from the intestinal tract in cases of sprue, but considers them to be of secondary, rather than of primary, importance.

The most extensive work has been that of Ashford.[13] On the basis of his observations he concluded that sprue was caused by infection of the gastrointestinal tract with a specific yeastlike fungus, *Monilia psilosis*. Anderson[14] was able to recover a similar organism from 1 case of sprue, whereas all the yeastlike fungi recovered from 65 stools from patients without sprue could be readily differentiated from this species by means of morphologic and cultural characteristics. The findings were also corroborated by Wood[15] and by Boyd,[16] but denied by Rogers.[17] Baumgartner and Smith[18]

have recently reported that they were able to recover *Monilia psilosis* from the majority of stools from 11 cases of sprue. Hannibal and Boyd,[19] however, recovered organisms conforming to Ashford's description of *Monilia psilosis* from 50 per cent of the stools from 44 patients, only 5 of whom were diagnosed as sprue, and Bovaird[20] was able to isolate *Monilia psilosis* from only 1 of 11 cases of sprue.

More recently Ashford[21] has modified his original conclusions and he now believes that sprue is a symptom complex produced by glandular insufficiency with a superimposed infection of the gastrointestinal tract with *Monilia psilosis*. This agrees more closely with the work of Smith.[22]

A corresponding divergence of opinion also exists as regards the importance of the presence of yeastlike organisms in the gastric contents. Zalesky,[23] Maresch[24] and many others have found these fungi in the gastric contents at autopsy, and have apparently believed that they were at least a contributing, if not the chief, cause of death. Askanazy[25] has been able to demonstrate, histologically and culturally, yeastlike fungi in nearly all of a large series of gastric and duodenal ulcers, and considers that secondary infections with such organisms is an important factor in the production of chronic ulcers. Moppert and Kagan,[26] however, have cultured the gastric contents from normal individuals and from a variety of diseased conditions, and, with one exception, found no striking difference in the incidence of yeastlike fungi. In cases with carcinoma of the stomach, the organisms were recovered from a very high percentage of cases. They concluded that these fungi are saprophytes, and that an increase occurs in conditions accompanied by a delayed evacuation time of the stomach.

Wood[15] has recently emphasized the clinical similarity between sprue and pernicious anemia, and has reported that *Monilia psilosis* was regularly found in the stools of 15 patients suffering from the latter disease, whereas in over 40 cases without sprue or pernicious anemia the organisms were never recovered. He was able to produce blood findings similar to those of pernicious anemia by feeding the fungi to guinea pigs and concludes that *Monilia psilosis* may be the etiologic factor of pernicious anemia. Warthin[27] and Broun[28] have repeated the experimental work and have failed to confirm the production of anemia. In 14 cases of pernicious anemia Baumgartner and Smith[18] obtained *Monilia psilosis* from the stools in only 3 cases (21 per cent); whereas in 17 cases of diarrhea the organisms were found in 5 cases (29 per cent).

It is evident that a great deal of confusion and divergence of opinion exists, not only in regard to the importance of the existence of yeastlike fungi in the gastrointestinal tract, but also in regard to the classification of isolated strains. Although the work reported in this paper was started primarily with the intention of investigating the relationship of infection of the gastrointestinal tract

with *Monilia psilosis* to pernicious anemia, it developed into a study of the yeastlike fungi in the gastrointestinal tract in a variety of conditions and an attempt to evaluate the importance of the findings.

Methods. The isolation of yeastlike fungi from stools or gastric contents is exceedingly easy, because of the fact that they will grow on a medium with an acidity usually sufficient to prevent growth of the ordinary intestinal bacteria. One loopful of the material to be examined was streaked on a plate of Sabouraud's agar* within four or five hours after being obtained. Such cultures were usually either negative or developed one or more types of yeastlike fungi. Occasional colonies of staphylococci and molds or other higher bacteria were sometimes found, but no difficulty was experienced in picking individual colonies of the yeastlike fungi. After forty-eight hours' incubation at 37.5° C., the number and type, or types, of colonies as confirmed by stained preparations, were noted and a characteristic colony of each type transplanted to a fresh plate of Sabouraud's agar. If this subculture appeared to be pure, after incubation, a transplant was made to infusion broth (pH ±7.6), in order to rule out the presence of contaminating bacteria unable to grow on the agar at pH 5.0. Slants of Sabouraud's medium were used for stock cultures. Each organism obtained from the stools or gastric contents was examined routinely in the following manner:

Morphologic Characteristics. *Cell Morphology.* The morphology of the cells was determined by examining, with an oil immersion, lens unstained cover-glass preparations of forty-eight hour cultures at 37.5° C. in 3 per cent dextrose beef extract broth (reaction unadjusted, pH ±6.5). The size and shape of the cells were noted, as well as the presence or absence of nuclei, vacuoles, granular cytoplasm, mycelia, etc.

Mycelia Formation. The formation of mycelia was determined by lightly inoculating a very thin film of 4 per cent dextrose beef-extract agar (pH 5.0) on a sterile cover glass. This was then inverted over a sterile glass ring, attached to a slide by means of balsam and containing about 10 drops of sterile salt solution in the bottom of the cell so formed. The upper rim of the glass ring was covered previously with sterile vaseline, and a "moist chamber" was thus formed. After twenty-four hours incubation at 37.5° C., the cultures were examined for mycelia and, if they were found, the presence or absence of septa and branching and the type of budding were noted. All strains failing to produce mycelia were grown for two successive generations in carrot infusion,† a medium shown by Draper[29] to be most favorable

* *Sabouraud's agar:*

Maltose, Difco	40 gm.
Bacto-peptone, Difco	10 "
Agar, chopped shreds	18 "
Glycerin	10 cc.
Water to make	1000 "

Filter through cotton. Tube in 100 cc. amounts and autoclave. Determine the amount of 10 per cent hydrochloric acid necessary to adjust one tube to pH 5.0, using methyl red as an indicator, and add this amount of acid to each tube after melting the agar, prior to pouring the plates. If the reaction is adjusted before autoclaving the medium will not solidify on cooling.

† *Carrot infusion:*

Carrots, finely minced	200 gm.
Water	120 cc.

Infuse at ice-box temperature for forty-eight hours. Filter, tube and autoclave.

for the production of mycelia. In several instances mycelial growth was obtained in the second carrot infusion culture of organisms which previously had shown no evidence of mycelia.

Ascospore Formation. In order to differentiate between true and imperfect yeasts the formation of ascospores was determined in the usual manner by heavily inoculating sterile gypsum blocks from twenty-four hour dextrose agar slants. The blocks were incubated at 30° C. for forty-eight hours, and unstained cover-glass preparations were then made from the surface scrapings.

In examining an unstained preparation of one of the strains from the surface growth of a seven-day-old gelatin stab, the presence of ascospores was accidentally observed. Subsequently all strains were similarly examined and 2 more ascospore producers were found, which had been missed by the gypsum block method.

Cultural Characteristics. *Sabouraud's Medium.* The appearance of individual colonies on plates of Sabouraud's agar after three to four days' incubation at 37.5° C. was observed.

Dextrose Broth. The type of growth in 3 per cent dextrose beef-extract broth (reaction unadjusted, pH = 6.5) after twenty-four hours' incubation at 37.5° C. was noted.

Gelatin Stabs. Beef extract gelatin (unadjusted, pH = 7.2) stabs were made, incubated at room temperature for fourteen days, and the type of growth observed.

Sugar Fermentations. Dunham fermentation tubes containing peptone water with 1 per cent Andrade's indicator and 1 per cent of the desired sugar (dextrose, levulose, maltose, saccharose, galactose or lactose) were used. The reaction was adjusted so that the medium was light pink in color when hot and colorless when cold. Chemically pure sugars were used, and the tubes were sterilized by the fractional method. They were incubated for five days* at 37.5° C. Slight to moderate increases in acidity were noted as "slight." The presence of a very small bubble of gas in the inverted tube was disregarded.

Results.. The results obtained by culturing 192 stools from 121 individuals and 31 gastric contents from 29 individuals, together with various clinical findings, are given in Table I. Seventy-eight strains of yeastlike fungi were isolated in pure culture. A single colony, or only a few colonies, were frequently found, and but little significance can be attached to their presence. In a subsequent analysis of the findings this point will be considered. The table also contains the morphologic and cultural characteristics of several named species, chiefly monilias, obtained from a variety of sources, of 3 strains freshly isolated from cases of thrush and of 1 strain obtained from the sputum of a case of miliary tuberculosis.

* The fermentation results obtained after five days' incubation were thought to be more accurate than those after fourteen days' incubation. In the first place, moderate amounts of gas, which were observed at the end of five days, always decrease and frequently disappear on incubation for the longer period, presumably on account of solution of the gas in the medium and subsequent diffusion from the surface. Secondly, when using disaccharides, which are fermented with the formation of acid, there is always the possibility, on prolonged incubation, of inversion or splitting and the monosaccharid so formed may be one which is fermented by the organism n question with the formation of acid and gas. Late gas formation is occasionally observed in acid saccharose tubes and is best explained by the latter objection.

TABLE I.

Case number.	Diagnosis.	Sex.	Age.	Habitat.	Diarrhea.	Achylia.	Red blood corpuscles.	Hemoglobin, per cent.	Colonies obtained. Stools		Number of colonies.	Morphology.	Mycelia.	Colonies on agar.	Growth in broth.	Growth in gelatin.	Sugar fermentations.						Classification.
									Stool.	G. C.							Dextrose.	Levulose.	Maltose.	Saccharose.	Galactose.	Lactose.	
							$\times 10^6$																
1	Pernicious anemia	M	51	−	+	+	0.9	20	−A	⊕	Many	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
2	Pernicious anemia	M	55	−	−	+++	1.0	24	ND	− − ⊕	Many	T	+++	T	C	++	AG	AG	AG	As	A	O	Parasaccharomyces A
4	Pernicious anemia	M	51	−	+	++	0.9	30	+	− − − −	3	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
7	Pernicious anemia	M	47	−	+	+	1.5	48	ND	− − ⊕ −	Many	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
8	Pernicious anemia	F	42	−	+	+	1.9	50	ND	⊕+	Many	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
9	Pernicious anemia	F	63	−	+	+	3.8	95	ND	−⊕	1	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
10	Pernicious anemia	F	61	−	+	+	1.5	45	ND	− − − −													
18	Pernicious anemia	M	57	−	+	+	1.2	30	ND	−⊕	10	A	+	A	C	+	AG	AG	O	AG	AG	AG	Parasaccharomyces D
19	Pernicious anemia	F	60	−	+	+	1.6	38	ND	⊕	Many	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
59	Pernicious anemia	M	60	−	+	+	1.8	52	ND	− − −													
64	Pernicious anemia	M	36	−	+	+	1.2	29	ND	− −													
73	Pernicious anemia	F	71	−	+	+	0.7	20	+A	⊕	Many	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
76	Pernicious anemia	F	58	−	+	+	1.2	35	−	− −⊕	3	A	+	T	C	+	AG	AG	AG	AG	AG	O	Endomyces A
77	Pernicious anemia	F	45	−	+	+	1.3	26	ND	−													
84	Pernicious anemia	M	49	−	+	+			ND														
93	Pernicious anemia	F	38	−	−	+	1.2	30	ND	⊕	8	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
114	Pernicious anemia	M	52	−	+	+	1.5	40	ND	⊕	3	T	+	T	C	+	AG	AG	AG	A	A	O	Parasaccharomyces A
129	Pernicious anemia	M	33	−	+	+	0.9	25	+	−													
11	Anemia of pregnancy	F	28	−	−	−	0.9	28	ND	⊕ − +−	1	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
13	Carcinoma of stomach	M	62	−	−	−			−	− −													
15	?Pernicious anemia	M	28	−	−	−	2.2	28	+	⊕	Many	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
16	Carcinoma of stomach	M	72	−	−	−	++		+	⊕+	1	A	+	T	SG	+	A	A	As	A	As	O	Parasaccharomyces F
17	Anemia of pregnancy	F	40	−	−	−	4.3	61	ND	⊕	Many	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
20	Typhoid fever	M	22	−	+	−		70	ND	−													
22	Carcinoma of cervix	F	32	−	−	−	3.0		ND	−													
23	Diabetes mellitus	F	50	−	−	−		75	ND	−													
24	Pulmonary tuberculosis	F	32	−	−	−		70	ND	−													
25	Exophthalmic goiter	F	23	−	−	−	4.5	75	ND	− −													
26	Pelvic cellulitis	F	31	−	−	−		70	ND	− −													
27	Rheumatic heart disease	M	14	−	−	−	4.1	71	ND	− −⊕	50	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
28	Aortitis	M	52	−	−	−	4.8	85	ND	− − − −													
29	Rheumatic fever	M	27	−	−	−	4.1	76	ND	−													
30	Chronic myocarditis	M	56	−	−	−	6.3	91	ND	− −													
31	Typhoid fever	M	23	−	+		2.4	40	ND	⊕+	a. Many	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
											b. 8	A	+R	A	SG	−	A	A	As	O	O	O	?Parasaccharomyces I

32	Chronic myocarditis	M	68	−	−			80	ND	−													
33	Cardiac decompensation	M	33	+	−			90	ND	−													
34	Catarrhal jaundice	M	28	+	−		4.3	92	ND	− −													
35	Erythema nodosum	F	27	−	−		4.3	85	ND	− − −													
36	Chronic myocarditis	M	62	−	−			96	ND	⊕	1	A	+	A	SG	+	AG	AG	O	O	O	O	Parasaccharomyces C
37	Chronic nephritis	M	25	−	−		2.5	62	ND	⊕	1	A	+	A	SG	+	AG	AG	As	O	As	O	Parasaccharomyces C
38	Hypertension	M	72	−	−		4.5	73	ND	⊕	15	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
39	Congenital heart disease	M	18	+	−		5.6	90	ND	⊕ + −	Many	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
40	Bronchopneumonia	M	47	−	−			80	ND	⊕ + +	Many	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
41	Chronic alcoholism	M	40	−	−		5.6	80	ND	−													
42	Chronic nephritis	M	51	−	−		5.0	47	ND	− − − −													
43	?Embryoma	F	72	−	−		3.6	29	ND	⊕ +	15	T	+	T	C	+	AG	AG	AG	O	A	O	Parasaccharomyces A
44	Lobar pneumonia	F	63	−	−			70	ND	−													
45	Bacterial endocarditis	F	29	−	−		3.1	55	ND	−													
46	Hypertension	F	53	−	−		6.3	100	ND	⊕	Many	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
47	Hemiplegia (right)	F	40	−	−			70	ND	⊕	1	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
48	Rheumatic heart disease	F	19	−	−		4.9	81	ND	−													
49	Lobar pneumonia	F	18	−	−			70	ND	−													
50	Chronic nephritis	F	29	−	−		4.2	88	ND	⊕	a. Several	A	+R	A	SG	−	A	A	As	O	O	O	?Parasaccharomyces I
											b. Several	A	+	A	SG	+	AG	AG	O	O	O	O	Parasaccharomyces C
51	Typhoid fever	M	21	+	−		4.8	95	ND	− −													
52	Duodenal ulcer	M	47	−	−			95	ND	−													
53	Arteriosclerosis, thrombosis right femoral artery	F	57	−	−	+	2.0	22	+	⊕ +	Many	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
54	Chronic bronchitis	M	69	−	−			87	ND	−													
55	Chronic myocarditis	M	50	− −	−		4.9	82	ND	−													
56	Acute catarrhal jaundice	M	35	+	−		6.1	86	ND	− −													
57	Acute pharyngitis	F	20	−	−		4.6	85	ND	⊕	2	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
58	Rheumatic heart disease	F	58	−	−			85	ND	⊕ − − −	3	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
60	Carcinoma of cecum	F	53	−	−		3.2	52	ND	−													
61	Colitis	M	40	−	+		4.4	63	ND	⊕	1	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
62	Tuberculous pleurisy	F	46	−	−	−	4.8	50	+	− − −													
63	Obesity	M	48	−	−	−	4.9	91	ND	⊕	1	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
65	Lobar pneumonia	M	31	−	−		4.9	87	ND	−													
66	Duodenal ulcer	M	42	−	−		3.6	60	ND	⊕ + − +	10	T	+	T	C	+	AG	AG	AG	O	A	O	Parasaccharomyces A
67	Uremia, chronic nephritis	M	50	−	−	+	2.8	35	+A	− −													
68	Tuberculous adenitis	M	29	−	−		5.0	88	ND	⊕	8	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
69	Lobar pneumonia	M	42	−	−		4.5	86	ND	− −													
70	Chronic nephritis	M	31	−	−		5.0	58	ND	− −													
71	Bronchopneumonia	F	38		−			77	ND	−													
72	Bronchopneumonia	F	98	−	−		3.6	49	ND	⊕ +	Many	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
74	Pulmonary tuberculosis	F	58	−	−		3.6	60	ND	− −													
75	Myelogenous leukemia	M	65	−	−		3.7	69	ND	−													
78	Lobar pneumonia	F	18	−	−			70	ND	−													
79	Pyelitis	F	32	−	−		4.5	72	ND	⊕	8	T	+	T	SG	+	AG	AG	AG	AG	A	O	Parasaccharomyces F
80	Pulmonary tuberculosis	M	73	−	−		4.3	71	ND	−													
81	Rheumatic heart disease	F	29	−	−		4.3	72	ND	⊕	1	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
82	Infectious arthritis	F	25	−	−		4.7	91	ND	− ⊕	2	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
83	Rheumatic fever	F	38	−	−			76	ND	−													

Case number.	Diagnosis.	Sex.	Age.	Habitat.	Diarrhea.	Achylia.	Red blood corpuscles.	Hemoglobin, per cent.	Colonies obtained. Stools. Stool.	Colonies obtained. Stools. G. C.	Number of colonies.	Morphology.	Mycelia.	Colonies on agar.	Growth in broth.	Growth in gelatin.	Sugar fermentations. Dextrose.	Levulose.	Maltose.	Saccharose.	Galactose.	Lactose.	Classification.
							$\times 10^6$																
85	Carcinoma of mediastinum	M	54	−	−				ND	−													
86	Influenza (convalescent)	M	56	−	−			90	ND	−													
87	Pyelitis	F	21	−	−		4.7	70	ND	− − ⊕	Several	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
88	Transverse myelitis	M	39	−	−				ND	− ⊕	Many	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
90	?Gastric ulcer	M	38	−	−	−			− −	− −													
91	Polycythemia vera	M	38	−	−		7.0	114	ND	⊕	6	A	+R	A	SG	−	A	A	O	O	O	O	?Parasaccharomyces I
92	Arteriosclerosis, hypertension	M	41	−	−		5.2	90	ND	−													
94	Chronic nephritis	M	29	−	−		4.0	60	ND	−													
95	Cardiac decompensation	F	45	−	−		4.4	75	ND	−													
96	Carcinoma of right lung	M	58	−	−		3.4	58	ND	⊕	30	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
97	Infectious arthritis	F	45	+	−	−	6.2	90	−														
98	Pulmonary emphysema	M	66	−	−		5.8	75	ND	−													
99	Cerebral arteriosclerosis	M	70	−	−		4.8	85	ND	⊕	7	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
101	Lobar pneumonia	F	65	−	−			70	ND	⊕	5	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
104	Lobar pneumonia	M	52	−	−			90	ND	−													
105	Arteriosclerosis, senility	F	80	−	−		5.1	45	ND	−													
106	Hysteria	M	19	−	−			87	ND	⊕	2	A	+	A	C	+	A	A	O	As	As	O	Parasaccharomyces E
107	Tuberculous kidney	M	18	−	−		3.5	62	ND	−													
108	Cerebral thrombosis	M	63	−	−		5.7	82	ND	−													
109	Lobar pneumonia	M	33	−	−		5.0	82	ND	⊕	1	A	+	A	C	+	A	A	O	As	O	O	Parasaccharomyces E
110	Chronic nephritis, uremia	M	31	−	−		3.1	51	ND	−													
111	Carcinoma of stomach	F	56	−	−	+	2.4	35	+	⊕	a. 4	T	+	T	SG	+	AG	AG	AG	AG	AG	O	Parasaccharomyces B
											b. Several	A	+	A	C	−L	A	A	As	O	As	O	Parasaccharomyces G
112	Secondary anemia (?cause)	F	55	−	−	+	4.2	35	+	⊕	5	T	+	T	C	+	AG	AG	AG	A	A	O	Parasaccharomyces A
124	Carcinoma of colon	M	60	−	−	+	3.6	36	+	− −													
126	Echinococcus cyst of spleen	M	59	+	−	−	3.8	63	+	−													
127	Colitis	M	38	−	−	−	6.2	125	+	−													
131	Sprue	M	65	+	+	−	0.9	25	+	⊕ +	10	T	+	T	C	+	AG	AG	AG	A	A	O	Parasaccharomyces A
132	Scurvy	M	43	−	−		3.8	35	ND	−													
133	Hemorrhoids, second anemia	F	49	−	−		2.5	30	ND	−													
14	Normal	M	28	−	−				ND	− −													
115	Normal	M	29	−	−				ND	−													
116	Normal	M	28	−	−				ND	−													
117	Normal	M	27	−	−				ND	−													
118	Normal	M	29	+	−				ND	⊕	3	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
119	Normal	M	26	−	−	−			+	⊕	1	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
120	Normal	M	33	−	−				ND	−													
121	Normal	M	29	−	−				ND	−													
122	Normal	M	25	−	−				ND	−													
123	Normal	M	25	+	−				ND	⊕	14	A	+	T	C	−	AG	AG	AG	AG	AG	O	Endomyces A

									Gastric Contents													
									Stool.	G. C.												
1	Pernicious anemia	M	51	−	+	+	0.9	20	+	−A												
4	Pernicious anemia	M	51	−	+	+	3.5	83	− − − − − − + −	⊕	Many	T	+	T	C	+	AG	AG	AG	A	A	O	Parasaccharomyces A
73	Pernicious anemia	F	71	−	−	+	0.7	20	+	⊕A	Many	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
76	Pernicious anemia	F	58	−	−	+	1.2	35	− − +	−												
113	Pernicious anemia	M	76	−	−	+	1.1	32	ND	⊕ −A	Many	T	+	T	SG	+	AG	AG	AG	AG	AG	O	Parasaccharomyces B
129	Pernicious anemia	M	33	−	+	+	0.9	25	−	⊕	Many	T	+	T	C	+	AG	AG	AG	A	A	O	Parasaccharomyces A
130	Pernicious anemia	F	62	−	−	+	0.9	25	ND	⊕	Many	T	+	T	C	+	AG	AG	AG	AG	AG	O	Parasaccharomyces B
5	Carcinoma of stomach	M	50	−	−	+	2.0	55	ND	⊕	a. Several	A	−	T	C	−	AG	AG	As	O	As	O	Cryptococcus A
											b. Several	A	+	A	SG	+	AG	AG	As	O	As	O	Parasaccharomyces C
12	?Duodenal ulcer	M	28	−	−	−			ND	−													
13	Carcinoma of stomach	M	62	−	−	+			− −	−													
15	?Pernicious anemia	M	28	−	−	+	2.2	28	+	⊕	Many	T	+	T	C	+	AG	AG	AG	A	As	O	Parasaccharomyces A
16	Carcinoma of stomach	M	72	−	−	+			+ +	⊕	a. Many	A	+	A	C	+	AG	AG	O	AG	AG	AG	Parasaccharomyces D
											b. Many	A	−	T	C	−	AG	AG	O	O	As	O	Cryptococcus A
53	Thrombosis rt. femoral vein, arteriosclerosis	F	57	−	−	+	2.0	22	+ +	⊕	Many	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
62	Tuberculous pleurisy	F	46	−	−	−	4.8	50	− − −	⊕	Many	A	−	A	C	−	O	O	O	O	O	O	Cryptococcus B
67	Chronic nephritis—uremia	M	50	−	−	+	2.8	35	− −	⊕A	Many	A	+	A	SG	+	AG	AG	O	O	O	O	Parasaccharomyces C
89	?Duodenal ulcer	M	32	−	−	−			ND	−													
90	?Gastric ulcer	M	38	−	−	−			−	− −													
97	Infectious arthritis	F	49	+	−	−	6.2	90	−	−													
100	Diabetes mellitus	M	60	−	−	−		85	ND	−													
102	Cellulitis of abdominal wall, toxemia of pregnancy	F	36	−	−	−	3.3	60	ND	⊕	Many	T	+	T	SG	+	AG	AG	AG	AG	AG	O	Parasaccharomyces B
103	Hemo-pneumo-thorax	M	18	−	−	−			ND	⊕	Several	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
111	Carcinoma of stomach	F	56	−	−	+	2.4	35	+	⊕	Many	T	+	T	SG	+	AG	AG	AG	AG	AG	O	Parasaccharomyces B
112	Secondary anemia — cause unknown	F	55	−	−	+	4.2	35	+	⊕	a. Many	T	+	T	C	+	AG	AG	AG	A	A	O	Parasaccharomyces A
											b. Several	A	+	A	SG	+	AG	AG	O	O	O	O	Parasaccharomyces C
124	Pleurisy with effusion	M	60	−	−	+	3.6	36	− −	⊕	Many	T	+	T	SG	+	AG	AG	AG	AG	AG	O	Parasaccharomyces B
125	?Carcinoma of gall bladder	M	53	−	−	+	4.1	72	ND	⊕	40	T	+	T	C	+	AG	AG	AG	A	A	O	Parasaccharomyces A
126	Echinococcus cyst of spleen	M	59	+	−	−	3.8	63	−	⊕	Many	A	+	T	C	−	AG	AG	AG	AG	AG	O	Endomyces A
127	Ulcerative colitis	M	38	−	+	−	6.2	125	−	⊕	Several	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
131	Sprue	M	65	+	+	−	0.9	25	+ +	⊕	Many	T	+	T	C	+	AG	AG	AG	A	A	O	Parasaccharomyces A
119	Normal	M	26	−	−	−			+	⊕	1	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A

Named Species.	Morphology.	Mycelia.	Colonies on agar.	Growth in broth.	Growth in gelatin.	Sugar fermentations.						Classification.
						Dextrose.	Levulose.	Maltose.	Saccharose.	Galactose.	Lactose.	
Monilia psilosis, No. 3 } Obtained from Dr. L. W. Smith, Boston	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
Monilia psilosis, No. 6 } Obtained from Dr. L. W. Smith, Boston	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
Monilia psilosis, No. 34a	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
Monilia psilosis, No. 117a	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
Monilia albicans, Elder } Obtained from Dr. B. K. Ashford, through kindness of W. C. Green, Boston	T	+	T	C	+	AG	AG	AG	O	As	O	Parasaccharomyces A
Monilia tropicalis, Castellani } Obtained from Dr. B. K. Ashford, through kindness of W. C. Green, Boston	T	+	T	SG	+	AG	AG	AG	AG	AG	O	Parasaccharomyces B
Monilia krusei, Castellani } Obtained from Dr. B. K. Ashford, through kindness of W. C. Green, Boston	A	+	A	SG	+	AG	AG	O	O	O	O	Parasaccharomyces C
Monilia macedoniensis, Castellani } Obtained from Dr. B. K. Ashford, through kindness of W. C. Green, Boston	A	+	A	SG	+	AG	AG	O	O	O	O	Parasaccharomyces C
Monilia psilosis, Kn.	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
Monilia psilosis, Ca.—sprue	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
Monilia psilosis, Be.—pernicious anemia	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
Monilia psilosis, Bir.—pernicious anemia	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
Monilia psilosis, McI.—pernicious anemia	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
Monilia psilosis, Do.—pernicious anemia	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
Monilia psilosis, Bis.—sprue	T	+	T	SG	+	AG	AG	AG	AG	AG	O	Parasaccharomyces B
Monilia psilosis, Si.—?sprue	T	+	T	C	+	AG	AG	AG	As	As	O	Parasaccharomyces A
Saccharomyces cerevisiæ, F.—Fleischmann's baker's yeast	A	−	T	C	−	AG	AG	AG	AG	AG	O	Saccharomyces
B-14-26—yeastlike fungus from typical thrush membrane	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
U-26-37—yeastlike fungus from esophageal membrane (infant—autopsy)	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
B-26-2541—yeastlike fungus from typical thrush membrane	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A
Yeastlike fungus from sputum (case of miliary tuberculosis)	T	+	T	C	+	AG	AG	AG	As	A	O	Parasaccharomyces A

ABBREVIATIONS:
SEX: M = male and F = female.
HABITAT: + = history of tropical or subtropical residence, and − = no such history.
DIARRHEA AND ACHYLIA: + = present and − = absent.
COLONIES OBTAINED: + = yeastlike fungi, − = no yeastlike fungi, ⊕ = strain or strains examined, ND = not done and A = autopsy.
MORPHOLOGY AND COLONIES ON AGAR: T = like *Parasaccharomyces A* and A = not like *Parasaccharomyces A*.
MYCELIA: + = present, − = absent and R = rudimentary.
GROWTH IN BROTH: C = growth in bottom of tube with clear supernatant fluid and SG = surface growth.
GROWTH IN GELATIN: + = lateral outgrowths, more marked at top ("inverted pine tree"), − = no lateral outgrowths and L = liquefaction.
SUGAR FERMENTATIONS: O = no fermentation, A = acid, As = slight to moderate acid and AG = acid and gas.

TABLE I.—SUMMARY OF GROUPS.

Parasaccharomyces A. Cells, round or oval (average size, 5 microns). In cultures containing many mycelia, elongated forms frequent. Cytoplasm, relatively clear with vacuoles containing refractive granules. Few nucleated cells. Septate mycelia.

On agar, colonies raised, round, shiny and white or creamy in color. In peptone water, granular growth in bottom of tube, with supernatant fluid clear and no pellicle. In gelatin stabs, coarse to fine lateral outgrowths. Ferment dextrose, levulose and maltose with the formation of gas. Acid always formed, but in varying amounts, in galactose and usually formed in saccharose. Lactose not fermented.

Parasaccharomyces B. Morphologically and culturally identical with *Parasaccharomyces A* except that in peptone water a very thin, oily growth always appears on the surface and that saccharose and galactose are always fermented with gas formation.

Parasaccharomyces C. Majority of cells elongated (2 to 3 x 5 to 6 microns). Cytoplasm granular. Few clear oval cells with vacuoles. Septate mycelia.

On agar, colonies flat, irregular, dull and white in color. In peptone water, majority of growth at bottom of tube, but some along sides of tube and some on surface, forming a very thin, oily scum. In gelatin stabs, coarse to fine lateral outgrowths.

Ferment dextrose and levulose with gas formation; never ferment saccharose or lactose. May, or may not, form a slight amount of acid in maltose and galactose.

Parasaccharomyces D. Cells oval (4 to 5 microns) with many elongated forms. Majority of oval cells clear with vacuoles, but a few are very granular. Elongated forms usually granular. Septate mycelia.

On agar, colonies raised, round, shiny and pale gray in color (semi-transparent)—old cultures show some brownish pigmentation. In peptone water, growth in bottom of tube with clear supernatant fluid and no pellicle. In gelatin stabs, fine lateral outgrowths. Ferment dextrose, levulose, saccharose, galactose and lactose with gas formation. Maltose not fermented.

Parasaccharomyces E. Cells oval (4 to 5 microns) with few elongated forms. Cytoplasm usually clear without vacuoles. Rare nucleated cell. Septate mycelia.

On agar, colonies flat, irregular, dull and white in color. In peptone water, growth at bottom of tube with clear supernatant fluid and without pellicle. In gelatin stab, fine lateral outgrowths. Ferment dextrose and levulose with the formation of acid. Maltose and lactose not fermented. A slight amount of acid is formed in saccharose and may, or may not, be formed in galactose.

Parasaccharomyces F. Cells predominantly elongated (1 to 2 x 3 to 7 microns) with few oval forms (3 to 4 microns). Former frequently contain large granules (usually bipolar); latter clear with occasional vacuoles. Septate mycelia.

On agar, colonies raised, regular, shiny and white in color. In peptone water, majority of growth at bottom of tube, but some along sides of tube and some on surface, forming a very thin, oily scum. In gelatin stab, lateral outgrowths. Ferments dextrose, levulose and saccharose with acid formation. Slight amount of acid formed in maltose and galactose. Lactose not fermented.

Parasaccharomyces G. Cells oval (4 to 5 microns). Few elongated forms and many septate mycelia. Cytoplasm slightly granular and contains vacuoles without refractive granules. No nucleated cells.

On agar, colonies raised, regular, shiny and dirty green in color. In

peptone water, growth at bottom of tube with clear supernatant fluid and no pellicle. In gelatin stab, liquefaction with marked mycelial production. Acid, without gas, produced in all sugars.

Parasaccharomyces I. Cells predominantly elongated (3 x 5 to 7 microns) with rare oval forms (3 to 4 microns). Cytoplasm usually clear with numerous vacuoles and occasional refractive granules. Mycelia very rudimentary, possibly merely chain formation of elongated forms.

On agar, colonies flat, irregular, dull, and white in color. In peptone water, growth in bottom of tube, but some along sides of tube and some on surface, forming a very thin, oily scum. In gelatin stab, no lateral outgrowths. Ferment dextrose and levulose with acid formation, slight acid formed in maltose. Saccharose, galactose and lactose not fermented.

In view of the formation of rudimentary mycelia and the absence of lateral outgrowths in gelatin stabs, these fungi may possibly belong to the genus, *Pseudomonilia*.

Cryptococcus A. Cells round or oval (3 to 5 microns). Cytoplasm clear with but few vacuoles and no refractive granules. No mycelia.

On agar, colonies raised, regular, shiny and white in color, but relatively small. In peptone water, growth at bottom of tube, with clear supernatant fluid and no pellicle. In gelatin stab, no lateral outgrowths, Ferment dextrose and levulose with acid formation. Slight acid formed in maltose and may, or may not, be formed in galactose. Saccharose and lactose not fermented.

Cryptococcus B. Cells round or oval (4 to 5 microns) with numerous nuclei. No mycelia.

On agar, colonies raised, regular, shiny and coral-pink in color. In peptone water, growth in bottom of tube with clear supernatant fluid and no pellicle. In gelatin stab, no lateral outgrowths. None of the sugars fermented.

Endomyces A. Cells round or oval (5 to 7 microns). Cytoplasm granular. Moderate number of small nucleated cells and a few elongated cells. Ascospores (2 to 4) formed on surface of gelatin stabs. No evidence of conjugation. Septate mycelia.

On agar, colonies raised, regular, shiny and white to creamy in color. In peptone water, growth at bottom of tube with clear supernatant fluid and no pellicle. In gelatin stab, one strain produced lateral outgrowths, whereas the other two failed to do so. Ferment dextrose, levulose, maltose, saccharose and galactose with gas formation. Lactose not fermented.

Much of the confusion which exists in the literature pertaining to the yeastlike fungi arises from the variety of generic names given to apparently identical organisms. For instance, *Oidium*, *Monilia*, *Saccharomyces*, *Endomyces*, *Parasaccharomyces* and *Blastomyces* are all used to name, apparently, the same fungus. The cryptogamic botanist, rather than the bacteriologist, is better qualified to attempt to untangle this maze of taxonomy. Anderson[14] has covered the ground thoroughly, and his key to the genera of budding fungi has been used for the classification of the strains isolated in this work.

But little need be said concerning the true or "perfect" yeasts. Only 3 strains were isolated which formed ascospores and, since all produced mycelia, they fall into the genus, *Endomyces*. The majority of the strains isolated fall into the group of asporogenic yeasts or *Fungi imperfecti*, and they may be divided, adopting the generic subdivisions of Anderson, in the following way:

I. Heavy dry pellicle formed on liquid media—*Mycoderma.*
II. No distinct pellicle formed.
  (*a*) Vegetative cells forming a septate mycelium under exceptional conditions, but predominantly budding—*Parasaccharomyces* (or *Monilia*).
  (*b*) Vegetative cells formed only by budding.
    1. Cells apiculate, limoniform—*Pseudosaccharomyces.*
    2. Cells frequently elongated into narrow nonseptate hyphal threads—*Pseudomonilia.*
    3. Cells typically yeastlike—*Cryptococcus.*

On the basis of morphology each strain has been assigned to one of the genera, as designated by Anderson. Similarly, a generic name has been given to the several named species of monilia and the 4 freshly isolated thrush and sputum strains used for comparison. From the table it will be noted that all of the strains, with the exception of the 3 of *Endomyces*, mentioned above, fall into 2 genera of the imperfect yeasts, *Parasaccharomyces* and *Cryptococcus*. All but 3 of these have been placed in the genus, *Parasaccharomyces*, which is more commonly termed *Monilia*. On the basis of morphologic and cultural characteristics the strains belonging to each genus have been separated into groups designated *A*, *B*, *C*, and so forth. No attempt has been made to identify individual species other than to classify the cultures of the named species according to this method. These groups are shown in the last column of Table I, and the morphologic and cultural characteristics of each group appear at the end of the table. The latter are summarized in Table II.

Although Anderson[14] obtained but few duplications among over 100 strains isolated in a similar way, it is evident from the table that 62 of the 78 strains fall into 3 distinct groups, *Parasaccharomyces A*, *B*, and *C*, the groups containing 50, 6 and 6 strains, respectively. The remaining 16 strains separate into 2 groups (? *Parasaccharomyces I* and *Endomyces A*) each containing 3 strains, 3 groups (*Parasaccharomyces D* and *E* and *Cryptococcus A*) each containing 2 strains and 4 strains (*Parasaccharomyces F*, *G* and *H* and *Cryptococcus B*) which are individually distinct. The morphologic and cultural characteristics of the members of each group were identical with the exception of slight variations in the amount of acid produced by 1 group in saccharose and by 4 groups in galactose. By employing only 2 or 3 of the basic characteristics investigated it was possible to divide the strains into groups, which still held true, when the other findings were taken into consideration. Contrary to the usual contention, all of these characteristics, with the exception of mycelia production and type of growth in gelatin stabs, have remained constant even after a year or more, provided that the various test media were inoculated with an actively growing broth culture.

TABLE II.

Classification.	Morphology.			Agar colonies.		Mycelia.	Ascospores.	Growth in broth.	Growth in gelatin	Fermentations.					
	No. strains.	Shape.	Cytoplasm	Type.	Color.					Dextrose.	Levulose.	Maltose.	Saccharose.	Galactose	Lactose.
Parasaccharomyces A	50	R-O	C	S-E	C	+	−	C	+	AG	AG	AG	O As A	As A	O
Parasaccharomyces B	6	R-O	C	S-E	C	+	−	SG	+	AG	AG	AG	AG	AG	O
Parasaccharomyces C	6	E	G	D-F	W	+	−	SG	+	AG	AG	O As	O	O As	O
Parasaccharomyces D	2	O-E	±G	S-E	G(B)	+	−	C	+	AG	AG	O	AG	AG	AG
Parasaccharomyces E	2	O-E	C	R-F	C	+	−	C	+	A	A	O	As	O As	O
Parasaccharomyces F	1	O-E	±G	S-E	W	+	−	SG	+	A	A	As	A	As	O
Parasaccharomyces G	1	O	±G	S-E	Gr.	+	−	C	−L	A	A	A	A	A	A
Parasaccharomyces H	1	O	C	S-E	C	+	−	C	+	AG	AG	AG	AG	A	O
?Parasaccharomyces I	3	E	C	D-F	W	+R	−	SG	−	A	A	O As	O	O	O
Cryptococcus A	2	R-O	C	S-E	C	−	−	C	−	AG	AG	As	O	O As	O
Cryptococcus B	1	R-O	C	S-E	P	−	−	C	−	O	O	O	O	O	O
Endomyces A	3	R-O	G	S-E	C	+	+	C	±	AG	AG	AG	AG	AG	O

ABBREVIATIONS:
SHAPE: R = round, O = oval, and E = elongated.
CYTOPLASM: C = clear and G = granular.
TYPE: S = shiny, E = elevated, D = dull, F = flat and R = rough.
COLOR: C = creamy, W = white, G = gray, B = brown, Gr. = green and P = pink.
MYCELIA: + = present, − = absent and R = rudimentary.
ASCOSPORES: − = absent and + = present.
GROWTH IN BROTH: C = clear supernatant without surface growth and SG = surface growth.
GROWTH IN GELATIN: + = lateral outgrowths, − = no lateral outgrowths and L = liquefaction.
FERMENTATIONS: AG = acid and gas, A = acid, As = slight to moderate acid and O = negative.

A discussion of the findings in several of the most important groups is given below:

Parasaccharomyces A. Fifty strains obtained from stools or gastric contents fall into one definite group. The individual cells were round to oval in shape and the cytoplasm was relatively clear. On Sabouraud's agar the colonies were round, raised, shiny and white to creamy in color. Mycelia were always formed in suitable media and in broth growth occurred at the bottom of the tube with the supernatant fluid remaining clear. An inverted pine tree was produced in gelatin stabs. Dextrose, levulose and maltose were fermented with the formation of acid and gas. Saccharose was usually fermented with the formation of varying amounts of acid. Varying amounts of acid were always produced in galactose and lactose was never fermented.

Identical findings were obtained with all but one strain of the named species of parasaccharomyces, *Monilia psilosis*. Furthermore, cultures of this group could not be differentiated from *Monilia albicans* (Elder) or from the 4 freshly isolated thrush and sputum strains.

Six representative cultures (4 G. C., 31 a, 39, 73, 73 G. C., and 127 G. C.) were sent to Dr. B. K. Ashford at the School of Tropical Medicine of the University of Porto Rico, San Juan, P. R., for identification. Dr. Ashford very kindly ran these strains through his regular routine for identification and in his reply[30] states: "I have no reason to believe from cultures that these subcultures of yours are anything but *Monilia psilosis*, but you must remember that the last word on differentiation of the intestinal monilia has not been said. There is no doubt that in my hands they were all slow in producing gas in maltose bouillon and several lacked the brilliancy and clearness of *Monilia psilosis*, but these are not points of sufficient importance to cause me to hesitate in stating that they have the appearance of *Monilia psilosis*." The slowness in producing gas in maltose bouillon, as noted by Dr. Ashford, was not observed in maltose peptone water. Gas was invariably formed in two to three days.

Monilia psilosis, according to Ashford[13] and various other investigators, always produces acid and gas in dextrose, levulose and maltose and occasionally in saccharose and galactose. Wood[15], however, believes that, if pure sugars are used, dextrose, levulose and maltose are the only sugars fermented with the formation of gas. These latter fermentation reactions coincide with those of *Parasaccharomyces A*.

The only important variable noted in this entire group was that of mycelia production. With some strains, particularly those freshly isolated, this property was marked, while with others it was demonstrated only with difficulty. In view of the fact that mycelia production can be readily enhanced by cultivation in a suitable medium, such as carrot infusion, it was felt that this particular biologic characteristic was not of sufficient constancy to warrant classification therefrom.

Because of the marked predominance of this group the morphology and the growth on Sabouraud's agar of all cultures are tabulated in Tables I and II as "T," typical, or "A," atypical, depending on whether or not they conform to the appearance of *Parasaccharomyces A*. Further descriptions of the atypical appearances will be found in the summary at the end of Table I.

Parasaccharomyces B. Six cultures were identical with this large group except that in liquid media a thin, oily surface growth occurred, and saccharose and galactose were always fermented with the formation of gas. According to previous descriptions of *Monilia psilosis*, these fungi might be included in this species; in fact, one of the named species, *Monilia psilosis* (Bis.), showed the same characteristics. In view of the two sharp differences, however, these fungi have been set aside as a separate group. The determined organism, *Monilia tropicalis*, also falls into this group.

Parasaccharomyces C. This group is represented by 6 cultures, together with the named species, *Monilia krusei* and *Monilia macedoniensis*. The biologic characteristics were well differentiated from those of the other cultures. According to Castellani's[3] table, *Monilia macedoniensis* should ferment only saccharose and galactose with the formation of acid and gas; with this culture, however, the fermentations, as well as all the other findings were identical with those of this group.

Parasaccharomyces H. One culture was isolated which differed from *Parasachromyces A* only by forming gas in saccharose. According to previous descriptions this strain would be classified as *Monilia psilosis*. The fact that 50 strains of *Parasaccharomyces A* and 11 named strains of *Monilia psilosis* failed in this respect seemed sufficient cause for not including the culture in the large group, *Parasaccharomyces A*.

Miscellaneous Groups. The remaining 15 cultures failed to correspond to any of the larger groups. Duplication, however, did occur. A description of the remaining groups and individual strains will be found at the end of Table I. Of the 78 strains isolated only 4 were found which failed duplication.

Correlation of Cultural and Clinical Data. A total of 192 stools from 121 individuals were cultured. Yeastlike fungi were found in 51 cases, or 42 per cent. This agrees closely with Anderson's[14] figure of 43 per cent in 147 cases. Similar organisms were recovered from 21 (72 per cent) of the gastric contents from 29 individuals. Moppert and Kagan[26] found 69 per cent positive in 113 cases. As they stand, however, these figures mean but little. In the first place, in many instances only one or several colonies were obtained from the loopful of stool or gastric contents; secondly, many cases were cultured several times before a positive culture was obtained. It was decided not to call a stool or gastric sample positive unless 10 *or more colonies per plate were obtained on the first culture.* This reduces the cases with positive stools to 18 (15 per cent). In view of the overwhelming predominance of *Parasaccharomyces A*, particularly in stool cultures, a record of their isolation in relation to the total number of cases has also been tabulated. These figures, as well as those appearing subsequently, are given in Table III. Reaction of the stools apparently influenced the incidence of strains, but had little, if any, effect on the type of organism recovered. The reaction of 29 consecutive stools was determined by means of litmus paper. Nine were acid and 4 were alkaline, and in each group, only 1 strain, both *Parasaccharomyces A*, was obtained. From 16 neutral stools 5 strains of *Parasaccharomyces A* and 4 strains of other species were isolated. The presence of gastric achylia had no effect on the reaction of the stool. Inquiry was made in each case as to whether or not there had been residence in tropical regions within recent years. As infections with the so-called "pathogenic" yeasts or yeastlike fungi are supposed to be more common in such localities, an increased incidence might be expected in the group giving a history of such residence. Although the number of examinations is small, the cultural results from cases with a

positive history fail to show any marked difference from those of the series as a whole. Stools were obtained from 16 cases with diarrhea. Four were positive. The percentage is somewhat higher than the average, but fails to indicate any marked influence of intestinal hyperactivity on the cultural results. The incidence of yeastlike fungi in stools from cases of pernicious anemia is somewhat higher than that in stools from cases of miscellaneous disease, but is comparable to the incidence in selected groups of cases with gastric achylia or severe anemia other than pernicious anemia. Only 1 strain (*Endomyces A*) was obtained from the stools of normal individuals; furthermore, this was the only stool strain which was not classified as *Parasaccharomyces A*.

TABLE III.

	Stool cultures.			Gastric content cultures.		
	Total number.	Number positive.	Per cent positive.	Total number.	Number positive.	Per cent positive.
All cases	121			29		
Yeastlike fungi		18	15		17	59
Parasaccharomyces A		17	14		8	28
Cases with history of tropical residence	10			3		
Yeastlike fungi		3	30		2	67
Parasaccharomyces A		2	20		1	33
Cases with diarrhea	16					
Yeastlike fungi		4	25			
Parasaccharomyces A		4	25			
Cases of miscellaneous disease	92			21		
Yeastlike fungi		13	14		12	57
Parasaccharomyces A		13	14		5	24
Cases of pernicious anemia	18			8		
Yeastlike fungi		4	22		5	71
Parasaccharomyces A		4	22		3	43
Normal individuals	11			1		
Yeastlike fungi		1	9		0	0
Parasaccharomyces A		0	0		0	0
Cases with achylia, other than P. A.*	8			10		
Yeastlike fungi		2	25		8	80
Parasaccharomyces A		2	25		4	40
Cases without achylia	10			12		
Yeastlike fungi		2	20		4	33
Parasaccharomyces A		2	20		1	8
Cases of severe anemia, other than P. A.*	19					
Yeastlike fungi		5	26			
Parasaccharomyces A		5	26			

* Pernicious anemia.

The cultivation of gastric contents gave quite dissimilar results. The incidence in cases with pernicious anemia is distinctly higher than in the group of miscellaneous disease. When the latter, however, is split-up according to the presence or absence of achylia, the cases without achylia show a relatively low incidence, whereas those with achylia show an incidence which is practically identical with that of the cases of pernicious anemia. In contrast to the classification of the cultures isolated from stools, less than one-half of the cultures from the gastric contents fell into the group, *Parasaccharomyces A*.

A comparison of the cultural findings of stool and gastric contents of identical cases should furnish evidence as to the reliability of the method. Both were cultured in 20 cases. In 4 cases the stools and gastric contents were negative, in 7 cases *Parasaccharomyces A* was recovered from both, and *Parasaccharomyces B* was found in both in 1 case. Five cases gave various organisms other than *Parasaccharomyces A* in the gastric contents with negative stools. Inspection of the results seems to indicate that numerous yeastlike fungi, which are unable to survive passage through the intestinal tract, may be ingested with food and be recovered from the gastric contents. Assuming that this is true, the findings in 17 cases were in complete accord. In 2 cases *Parasaccharomyces A* was found in the gastric contents with negative stools, and in 1 case the reverse was true.

Discussion. The outstanding feature of the results of stool culture is that *Parasaccharomyces A* was, with one exception, the only yeastlike fungus recovered on the first attempt and in appreciable numbers. As has been mentioned before, members of this group could not be differentiated from *Monilia psilosis*, and Dr. Ashford has identified 6 representative strains as *Monilia psilosis*. Furthermore, these strains are apparently identical with *Monilia albicans* (Elder) and with 3 cultures isolated from thrush membranes and 1 from the sputum. In spite of the fact that large numbers of other genera were recovered, in several instances, from the gastric contents, corresponding strains were never found in stools obtained from the same individuals. This would seem to signifiy that *Parasaccharomyces A* for some unknown reason is peculiarly adapted for growth, or survival, in the intestinal tract.

While it is true that the incidence of positive stool cutures is somewhat higher in pernicious anemia than in a large group of miscellaneous diseases, a similar increase was found in selected cases of severe anemia and gastric achylia, other than pernicious anemia. Although Baumgartner and Smith[18] recovered *Monilia psilosis* on first culture from the stools in 21 per cent of their cases of pernicious anemia, they found the same organism in 29 per cent of their cases with diarrhea. The fact that in this series only a small number of stools were cultured may explain the absence of positive cultures in normal individuals, for, in the group of miscellaneous disease, numerous cultures were obtained from cases in which the diagnoses—such as hypertension, bronchopneumonia, rheumatic heart disease, congenital heart disease, and so forth—certainly did not indicate any abnormality of the gastrointestinal tract.

This inability to differentiate between certain strains of yeastlike fungi isolated from the stools and gastric contents in various diseased and normal conditions of the gastrointestinal tract and strains of *Monilia psilosis* was experienced by Hannibal and Boyd.[19] Seventeen strains isolated from the stools in diseases other than

sprue were apparently identical with 5 sprue strains. Kohlbrugge,[7] in 1901, acknowledged that organisms similar to those found in sprue could be recovered from the stools in practically all cases with diarrhea, although they were never present in such large numbers nor could they be obtained from tongue scrapings. Ashford[30] has found that 3.5 per cent of the normal population in Porto Rico are carriers. Anderson,[14] on the other hand, claims that the yeasts isolated from cases other than sprue can be readily differentiated from Ashford's strain. Boggs and Pincoffs[31] studied a strain obtained from sputum which they considered to be indistinguishable from *Monilia psilosis;* and the biologic characteristics of cultures from thrush membranes and throats of diphtheria suspects obtained by Fineman[4] coincide with those of *Parasaccharomyces A*.

It seems likely that the organisms, which in this work have arbitrarily been classified as *Parasaccharomyces A*, are of relatively common occurrence in the mouth and gastrointestinal tract, and that their presence has little, if any, clinical significance. In conditions of general debility, such as severe malnutrition in young infants, or cachexia, secondary to malignant disease, in older people, the normal defenses of the body are broken down and these yeastlike fungi are able to invade the oral mucosa, producing the typical membrane of thrush. Frequently similar membranes are found in the esophagus and stomach, rarely in the intestine, and occasionally the organisms are able to invade the blood stream and produce metastatic abscesses in various parts of the body.

The fact that Askanazy[25] has been able to demonstrate yeastlike fungi in the mucosa and submucosa surrounding gastric and duodenal ulcers would seem to indicate simply a localized lowered resistance. There is really no more reason for considering the fungi of importance in the production of chronic ulcers than the various bacteria which are usually demonstrable in such lesions. In conditions of achylia a perfectly innocuous increase of the organisms in the gastric contents would be expected on account of the absence of the normal gastric secretion, which must possess some fungicidal properties. In diseases in general, either because of large numbers in the stomach, secondary to achylia, or because of debility, conditions may be more favorable for the growth, or survival, in the intestinal tract of this one large group of fungi, and one would reasonably expect to recover them more frequently from the stools.

A well-known point in regard to *Monilia psilosis*, which has been employed in differentiating this organism from other species of monilia and from other genera, is that rabbits are invariably killed by the intravenous injection of suitable amounts of culture. The most striking lesions found at autopsy are those of the kidneys, in whose cortices hundreds of miliary abscesses are found.

The pathogenicity of all strains of *Parasaccharomyces A*, which

were tested in this respect, corresponds to that of *Monilia psilosis*. Four, isolated from routine cultures (2 cases of pernicious anemia, 1 of typhoid fever and 1 of congenital heart disease), killed in doses ranging from 5 to 20 million per 1800 gm. body weight. The fatal doses of the 3 strains obtained from thrush membranes varied from 2 to 20 million, and those of 2 named strains of *Monilia psilosis* (Si., Wood, and No. 34a, Ashford) were 40 and 100 million, respectively.* Representatives of all the other groups containing 2 or more strains were, with one exception, apparently perfectly innocuous in doses as high as 100 million per 1800 gm. body weight. With this dose a strain (No. 130 G. C.) of *Parasaccharomyces B*, the group most closely allied to *Parasaccharomyces A*, was able to kill irregularly. Although 2 million per 1800 gm. body weight of a certain strain of *Parasaccharomyces A* will kill a rabbit, if injected intravenously, 100 million can be injected intraperitoneally without harm. These experiments will be reported in more detail in a subsequent paper.

The experiments briefly referred to above would seem to indicate that this group of yeastlike fungi is not particularly pathogenic for rabbits. The minimal lethal intravenous doses are relatively large and the invasive powers are very slight. This is further evidenced by the cause of death. As has been said, many miliary abscesses are always found in the kidney cortex. While it is true that similar abscesses are frequently found in other organs, they are never found as consistently or in such large numbers. For some unknown reason the organisms in the blood stream are apparently held back by the capillaries of the renal cortex more readily than by capillaries in other parts of the body. This blocking is followed by abscess formation and destruction of the surrounding renal parenchyma. If only a few abscesses occur, they increase in size up to a certain point and then heal with the formation of scar tissue. The uninvolved cortical tissue is able to carry on renal function perfectly. If, on the other hand, the abscesses are numerous, kidney function is so impaired that uremia ensues and the animal dies. The symptoms are always typically those of uremia —anuria, convulsions and marked increase in blood nonprotein-nitrogen (135 to 150 mg. per 100 cc. blood). No histologic evidence can be found which points to any cause for death other than this more or less mechanical interference with renal function.

The other strains of fungi, which have been recovered, are apparently of but little importance. It is very well known that such fungi are widely distributed in Nature. They are frequently found on overripe or decaying fruit and other foodstuffs, and it is only

* Although the date of isolation of these strains was not known, they must have been cultivated on artificial media for a much longer period of time than any of the other strains tested. This would probably account for the relatively large lethal doses.

natural that numerous strains should be recovered from the gastric contents, particularly in conditions of achylia, where the normal fungicidal acidity is lacking. Conditions in the small and large intestines, however, are such that they rarely occur in the feces, except in small numbers. Animal experiments seem to indicate that this group has little, if any, pathogenicity, at least for rabbits.

It remains for the cryptogamist to decide whether or not these fungi, which have been recovered from a great variety of clinical conditions and have been grouped as *Parasaccharomyces A*, are identical with *Monilia psilosis* and the organism most commonly recovered from thrush membranes. This unity of species is certainly indicated by the reported observations, but it is felt that the study has not been sufficiently comprehensive to warrant final judgment. For the same reason, no species names have been given. Serial letters have been used merely to differentiate groups which are morphologically and culturally similar. It seems that, in the past, every yeastlike fungus isolated from the throat, sputum or stool has been given a new species name, without comparison with previous strains, and has been called "pathogenic" merely because it was recovered from a diseased condition and produced fatal lesions in rabbits on intravenous injection. This has led to marked confusion and duplication, and many of these so-called "pathogenic" fungi are undoubtedly purely secondary invaders.

It has been impossible to confirm Wood's[15] findings—namely, that *Monilia psilosis* can be recovered from all cases of pernicious anemia and is never found in other diseases excepting sprue. These observations agree with those of Baumgartner and Smith.[18] If the group, *Parasaccharomyces A*, is identical with *Monilia psilosis*, it seems likely that the latter is unimportant as an etiologic factor, not only in pernicious anemia, but also in sprue. Marked increase of the fungi in sprue in the gastrointestinal tract, secondary to debility, gastric achylia, or some other cause, might lead conceivably to the liberation of irritating or harmful toxins, but experimental work, to be subsequently reported, has failed to indicate the existence of such toxins, either as exotoxins or endotoxins.

Conclusions. 1. Cultures of stools and gastric contents from a variety of diseases have yielded numerous strains of yeastlike fungi.

2. By far the majority of these strains, on the basis of similarity of morphologic and cultural characteristics, have been placed in the single species group, *Parasaccharomyces A*.

3. The members of this large group cannot be distinguished from named strains of *Monilia psilosis* or from yeastlike fungi isolated from typical thrush membranes or sputum and are apparently of common occurrence in the human gastrointestinal tract.

4. The two outstanding features of the correlation of cultural and clinical data are: (*a*) A higher incidence of yeastlike fungi in

the gastric contents from patients with gastric achylia, and (*b*) the failure to isolate species groups, other than *Parasaccharomyces A*, in appreciable numbers from the stools.

5. The percentage isolations of *Parasaccharomyces A* from the stools and gastric contents in pernicious anemia were no greater than those in cases with severe anemia and gastric achylia, other than pernicious anemia.

6. On the basis of these observations it seems likely that *Monilia psilosis* is unimportant as an etiologic factor, not only in pernicious anemia, but also in sprue.

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BIBLIOGRAPHY.

1. Langenbeck, B.: Frorieps Notizen, 1839, No. 252; cited by Kehrer, F. A.: Ueber den Soorpilz, Heidelberg, 1883.
2. Fischer, B., and Brebeck, C.: Zur Morphologie, Biologie und Systematik der Kahmpilze, der Monilia candida und des Soorerregers, Jena, 1894.
3. Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, New York, 1919.
4. Fineman, B. C.: Infect. Dis., 1921, **28**, 185.
5. Brünstein, A.: L'oidium albicans dans la bouche des personnes saines, Thèse de Genève, 1907, No. 151; cited by Askanazy, M.: Virchow's Arch. f. path. Anat., **234**, 111.
6. Casagrandi, O.: Centralbl. f. Bakteriol., 1898, **24**, 758.
7. Kohlbrugge, J. H. F.: Arch. f. Schiffs und Tropen-Hyg., 1901, **5**, 394.
8. Le Dantec, A.: Compt. rend. Soc. de biol., 1908, **64**, 1066.
9. Bahr, P. H.: A Report on Researches on Sprue in Ceylon, Cambridge, 1915.
10. Haan, J. de: Geneesk. Tijdschr. v. Ned.-Ind., 1902, **42**, 311.
11. Scheer, A. van der: Handbuch der Tropenkrankheiten, 1914, **3**, 451.
12. Castellani, A.: Trop. Med. and Hyg., 1914, **17**, 305.
13. Ashford, B. K.: J. Am. Med. Assn., 1915, **64**, 810, 1893; Am. J. Med. Sci., 1915, **150**, 680; 1916, **151**, 520; 1917, **154**, 157.
14. Anderson, H. W.: J. Infect. Dis., 1917, **21**, 341.
15. Wood, E. J.: Am. J. Med. Sci., 1925, **169**, 28.
16. Boyd, M. F.: South. Med., 1920, **13**, 229.
17. Rogers, L.: Indian Med. Gaz., 1918, **53**, 121.
18. Baumgartner, E. A., and Smith, G. D.: Am. J. Trop. Med., 1926, **6**, 433.
19. Hannibal, E. A., and Boyd, M. F.: Am. J. Trop. Med., 1921, **1**, 165.
20. Bovaird, D.: J. Am. Med. Assn., 1921, **77**, 753.
21. Ashford, B. K.: Am. J. Trop. Med., 1922, **2**, 139; Am. J. Med. Sci., 1923, **165**, 157.
22. Smith, L. W.: J. Am. Med. Assn., 1924, **83**, 1549.
23. Zalesky, N.: Virchow's Arch. f. path. Anat., 1864, **31**, 426.
24. Maresch, R.: Ztschr. f. Heilk., 1907, **28**, 145.
25. Askanazy, M.: Rev. méd. de la Suisse Romand., 1920, **40**, 477; Virchow's Arch. f. path. Anat., 1921, **234**, 111.
26. Moppert, G. G., and Kagan, J.: Rev. méd. de la Suisse Romand., 1922, **42**, 505.
27. Warthin, A. S.: Proc. Assn. Exp. Path., Cleveland, December, 1926 and personal communication.
28. Broun, G. O.: Proc. Am. Soc. Clin. Invest., Atlantic City, May, 1926; J. Clin. Invest., 1925–1926, **2**, 607.
29. Draper, A. A.: J. Infect. Dis., 1924, **34**, 631; 1925, **36**, 484.
30. Ashford, B. K.: Personal communication.
31. Boggs, T. R., and Pincoffs, M. C.: Bull. Johns Hopkins Hosp., 1915, **26**, 407.

BRONCHOGRAPHY.

Introduction of Iodized Oil into the Tracheobronchial Tree by the "Passive" Method.

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Since the first attempt at bronchography which was done by Chevalier Jackson in 1905, at which time bismuth oxid was insufflated into the tracheobronchial tree through the bronchoscope, many substances have been used as contrast media. Jackson now employs bismuth subcarbonate powder and prefers to introduce it into the bronchus through the bronchoscope. Working experimentally, Springer, in 1906, used an iodoform and bismuth powder in dogs; Telemann in 1913 employed barium sulphate solution in rabbits. Following the therapeutic use of iodin, applied through the bronchoscope to bronchiectatic cavities, Yankhauer, in 1917, was able to obtain a radiographic outline of the cavity. Lynah and Stewart used an emulsion of bismuth subcarbonate and olive oil as a contrast medium. In 1919, Weingärtner used anhydrous thorium oxydate in 3 patients. Bronchography, however, was not extensively used until Sicard and Forestier in 1922, working with Leroux, first introduced the iodized oil, Lipiodol, into the tracheobronchial tree. Since the introduction of this contrast medium, bronchography has been used much more frequently and more extensively. Quite recently Dyroff, a gynecologist, has advocated the use of a bromin combination in oil, which he terms "contrastol."

Many different methods have been employed to introduce these various contrast media into the tracheobronchial tree. Jackson originally used the bronchoscope for this purpose, and he, Clerf, Ballon, and other bronchoscopists still prefer this method of introduction. Most authors prefer the transglottic method, however. Sicard and Forestier, Besançon, Weil, Bernard and Azoula in France; Egan, Kovats, Abramowitsch and Tischomirow in Germany; Tagliabue in Italy; Moeller and Magnus, Danielson and Manfred and Grill in Sweden; Brunfin in America introduce a contrast medium by means of a laryngeal cannula. Lorey in Germany employs a rubber tube, on the end of which is a metal olive, which is introduced into the larynx. Lenk and Haslinger, Beck and Sgalitzer in Vienna, also, introduce a rubber tube into the larynx preparatory to the injection of an iodized oil. Wierig, in order to fill only a desired portion of the tracheobronchial tree, employs a tube similar to that used by Lorey. The metal olive, instead of

being left in the larynx, is introduced down into one of the primary divisions of the bronchi. Iglauer has recently described an ingenious modification of an intubation cannula, which is inserted into the larynx and through which the contrast medium may be injected. Armand-Delille and his coworkers prefer the intercricothyroid method. They have devised a special needle, quite similar to a tracheotomy tube, which is especially useful in children. Sicard and Forestier occasionally employ this method, while Grady, Hedblom and Head in this country and Guy and Elder in the British Isles prefer it. Caussade and Tardien, Pritchard and his coworkers favor the supraglottic method, which consists of introducing the iodized oil after anesthetization of the pharynx into the supraglottic region. Singer employs much the same procedure, but instead of anesthetizing the pharyngeal mucosa the tongue is pulled forcefully forward.

While working under Professor Clairmont in Zurich, Switzerland, one of us observed a case which led to the "passive" introduction of contrast media into the trachea. A patient with carcinoma of the esophagus had a pharyngeal cocainization done preparatory to doing an esophagoscopy. Immediately following the esophagoscopy the patient was given a barium solution under the fluoroscope. Quite contrary to expectation, the contrast medium passed entirely into the larynx and trachea instead of into the esophagus. After a severe coughing paroxysm the entire solution was expectorated. The possibility of a perforation of the carcinoma into the trachea was considered, but it was ruled out by subsequent gastrointestinal examinations, esophagoscopy and bronchoscopy. It was then found that after complete anesthetization of the pharynx anything taken into the pharynx would pass into the trachea rather than into the esophagus. This method was described by Nather and Sgalitzer in 1925. Following this observation we have used this simple technique for the introduction of contrast media into the tracheobronchial tree, as described below.

Technique. No preliminary medication is necessary. The patient is allowed to eat as usual. He is instructed to brush his teeth well and to use an antiseptic mouth wash. The anterior surface of both anterior faucial pillars is swabbed with a 10 per cent cocain solution. In less than 10 per cent of cases, it is necessary to anesthetize the posterior pharyngeal wall in addition to the anterior pillars. It is essential, however, not to get the anesthesia too deep in the region of the upper esophageal orifice. The degree of anesthesia is determined by the mobility of the larynx. As soon as the larynx upon attempted deglutition remains immobile the anesthesia is complete. This requires from one to three swabbings with 10 per cent cocain solution. No adrenalin is used in the cocain solution, because only a temporary anesthesia is desired. The anesthesia obtained wears off within two to three minutes,

thus eliminating the danger of aspirating any other substance. Because of this only temporary anesthesia, it is essential to place the patient under the fluoroscopic screen immediately after the completion of the anesthesia. He is instructed to take the iodized oil (1 to 2 ounces), which is previously warmed, into his mouth. The head is tipped backward, and the body leaned slightly to the side which one desires to fill. In this position the patient is instructed to take short breaths, during which time the iodized oil is aspirated into the trachea. This entire procedure is done under the fluoroscope and the mode of filling of the tracheobronchial tree very carefully observed. We heartily agree with Lenk and Haslinger that the fluoroscopic examination in these cases is more important than the interpretation of the plates. During fluoroscopy, the patient is turned in different directions, thus eliminating the possibility of making a false diagnosis of dilatation of the bronchial tree, due to the superimposition of two bronchi. Occasionally one finds that the alveoli fill so quickly that a haziness, which obscures the underlying bronchial picture, is produced (Fig. 6). In this way a bronchial dilatation may be overlooked if the Roentgen ray plate alone is relied upon.

Reactions. The patient's reaction to this procedure varies with the pathology encountered. An individual with a perfectly normal tracheobronchial tree possessing a normal cough reflex will cough as soon as the iodized oil reaches the first primary divisions of the bronchi. This cough reflex can be easily controlled, however, by the "passive" introduction of 3 per cent novocain solution, as advocated by Sicard and Forestier. Those individuals, however, who present pathology in the tracheobronchial tree, especially those having large amounts of secretion, act quite differently. The tracheobronchial tree is accustomed to the presence of a large amount of secretion, so that the normal cough reflex is lost. In this type of case the iodized oil enters the tracheobronchial tree and causes no disturbance whatever, aside from an occasional slight dyspnea, which is only temporary. We have noticed no other reactions. We now use about 4 cc. of a 3 per cent novocain routinely before introducing the contrast substance because in this way in the patient with a normal cough reflex an anesthesia is produced. In the individual whose tracheobronchial tree is filled with secretion the anesthetic solution is enough to cause an overflow which results in a cough emptying the tracheobronchial tree. In our series of over 700 cases, we have never noticed any signs of cocain intoxication following the anesthetization of the pharynx, even though we have been constantly on the lookout for it.

If the filling of an upper lobe is desired, the above technique is carried out, but the patient is seated before the fluoroscope and as soon as the iodized oil is seen entering the trachea he is tipped to the affected side to a position in which the shoulders are lower than

the pelvis. In this position, the oil flows by gravity and is aspirated into the upper lobe. Stereoroentgenograms should be made immediately after the completion of the fluoroscopic examination, not for diagnosis but for confirmation and record.

Physiology. Swallowing is a reflex act. The first portion is voluntary, whereas the remaining portion is involuntary. Following mastication, the food is thrown into the pharynx by the elevation of the tongue, which is a voluntary act. When the food passes the fauces, it initiates an impulse which is responsible for the involuntary or reflex act of swallowing. Centripetal impulses are carried to the medulla and centrifugal impulses are in turn carried back to the pharynx from the medulla. A contraction of the pharyngeal muscles is thus brought about. Coincident with this phenomenon there is an elevation of the larynx to a position beneath the base of the tongue so that the superior laryngeal opening is protected by the epiglottis and the base of the tongue (Fig. 1). According to Killian, there is a normal tonicity of the upper esophageal orifice which becomes relaxed during deglutition, as a result of an inhibitory impulse supplied to it. Thus, when food enters the pharynx, the reflex act of swallowing is instituted, the pharyngeal muscles contract, the larynx becomes elevated to a point of safety, and the tonically contracted esophageal orifice becomes relaxed. If a sensory anesthesia of that portion of the pharynx where this reflex act is instituted is produced, a substance passing into the pharynx will not initiate the reflex of swallowing. This we do by the cocainization of the anterior faucial pillars. Following the anesthesia as described above, the oil in passing into the pharynx, which is a region common to both the respiratory and digestive tracts, does not initiate the act of swallowing; the larynx does not move upward to a point of safety beneath the epiglottis and tongue; the upper esophageal orifice does not become relaxed, so the iodized oil can enter the only one remaining opening—the larynx. As brought out previously, it is essential not to anesthetize the pharynx too completely, especially not in the region of the esophageal orifice, as the relaxation of an esophageal orifice can thus be produced.

Uses of Bronchography. The diagnostic possibilities of bronchography have been repeatedly emphasized. Yet because of the complexity of the methods employed in introducing the contrast media into the tracheobronchial tree, the procedure has been used in comparatively few and selected cases. Those individuals with chronic pulmonary symptoms have been given the benefit of this diagnostic procedure in the past, only if their symptoms were severe enough to warrant employing formidable procedures. A large group of cases presenting symptoms of a chronic infection of the respiratory tract have been allowed to go on, because the physician in charge did not consider the symptoms severe enough to justify such a procedure. On the other hand a large number of patients who were

too ill to be subjected to any operation which might cause a progression of their pathologic process have been denied the advantage of a positive diagnosis which is very often made possible by bronchography. As a diagnostic procedure, bronchography is most useful in the early obscure pulmonary conditions. In the advanced forms it may be used confirmatively but it is usually not necessary to make a positive diagnosis. A good history and physical examination will most commonly accomplish this. Bronchography is of greatest value in the early chronic pulmonary conditions, such as chronic bronchitis, recurrent bronchitis. etc., in which the exact etiology is not known. We have found a surprisingly large number of bronchiectases in individuals who have no history or positive physical or Roentgen ray findings typical of this condition. They are young students who are apparently well but do suffer from recurrent colds.

Case Reports. CASE I.—I. Z., female student, aged twenty-five years, was first seen in the student clinic on October 30, 1925. She gave a history of having had recurrent attacks of bronchitis; otherwise has been perfectly well.

November 28, 1925. Caught cold. Acute bronchitis.

January 9, 1926: Pain and stiffness in the back of the neck. Had noticed some pain in the right side of the chest, especially when lying on that side.

March 3: Acute bronchitis, which responded well to medical therapy.

April 15: Cough was more marked.

October 12: Acute bronchitis.

October 20: Bronchography, left lower lobe bronchi filled. Definite saccular dilatation (Fig. 2).

November 1: Patient felt very much improved. Sputum was about the same in amount but was expectorated more freely.

November 8: Coughed only once or twice in twenty-four hours. No morning cough.

November 17: Had gained 3 pounds in weight. Cough and sputum had decreased. Right lower lobe filled with iodized oil. Definite saccular dilatation (Fig. 3).

December 8: Slept all night without coughing. Coughed only at noon.

December 15: Bronchography left lower lobe.

January 5, 1927: Bronchography right lower lobe. Improvement was continuing.

March 18: Bronchography right lower lobe.

April 8: Left lower lobe filled with iodized oil.

May 6: Right lower lobe filled. Felt fine. Was carrying all her work in the university and in addition serving in the capacity of policewoman.

CASE II.—K. M., female, student, aged sixteen years, first seen in the student clinic on September 27, 1926. She gave a history of having had chronic bronchitis for years. Never had been incapacitated, however. Was able to carry on her school work perfectly satisfactorily.

November 3, 1926: Acute bronchitis.

December 3: Acute exacerbation of chronic bronchitis.

February 11, 1927: Bronchography, according to the passive technique. Fusiform and saccular dilatation of the proximal bronchi of the right lower lobe (Fig. 4).

February 25: Bronchography, left lower lobe. Normal tracheobronchial tree.

March 11: Patient was considerably relieved. Coughed only in the forenoon. Slept better. Had more pep than before. Right lung filled with iodized oil.

April 1: Improvement continued. Bronchography right lung.

April 29: Had no cough. Slept well. Bronchography, right lower lobe. Dilatation of bronchi was much less.

Comment. Both of these patients were young adults in apparently good physical condition. Neither their history, physical findings, nor roentgenograms of the chest would have suggested a diagnosis of bronchiectasis. Both have a marked dilatation of the tracheobronchial tree.

Every individual who has recurrent attacks of "bronchitis," "chronic bronchitis," or a suspected pulmonary tuberculosis with negative sputum should be given the advantage which this diagnostic procedure offers, providing, the procedure can be carried out in such a way that it is neither deleterious nor unpleasant for the patient. The "passive" introduction of contrast substances into the tracheobronchial tree is neither unpleasant nor strenuous for the patient. In none of our cases has a single patient objected to a refill. How often can this be said of the other procedures?

Equally as important as the diagnostic value of introducing iodized oil into the tracheobronchial tree are the therapeutic effects obtained. This fact has been recognized by many observers (Lenk and Haslinger; Moeller and Magnus; Sgalitzer; Abramowitsch and Tichomerow; Armand-Delille and Gelston; Grady; Sicard and Forestier; Lorey; Danielson and Manfred; Nicaud and Dollfus; Besançon, Weil, Bernard, and Azoulay; Jacoboeus; Fiessinger and Lemaire; Pritchard, White and Gordon).

Archibald and Brown deny that the intratracheal introduction of iodized oil has any therapeutic effect. As they employ the bronchoscopic method of introducing the iodized oil it can readily be seen that a repetition of the procedure would probably be objected to by the patient. While a single introduction of oil is often of a distinct benefit to a patient suffering from a chronic suppurative process in

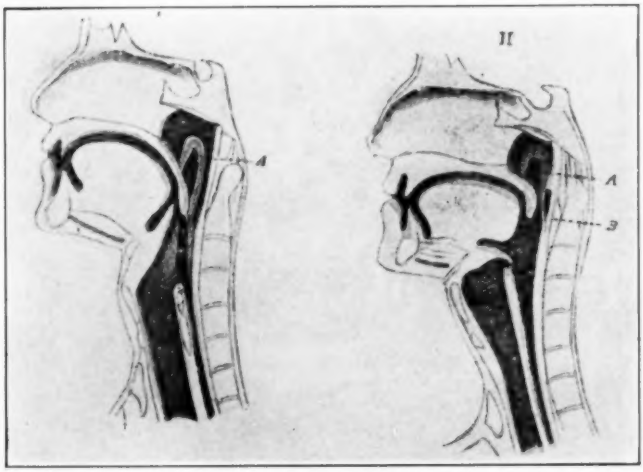

FIG. 1.—Showing elevation of the larynx during deglutition. The diagram is not absolutely correct, in that during rest the upper esophageal orifice is tonically contracted. (From Starling.)

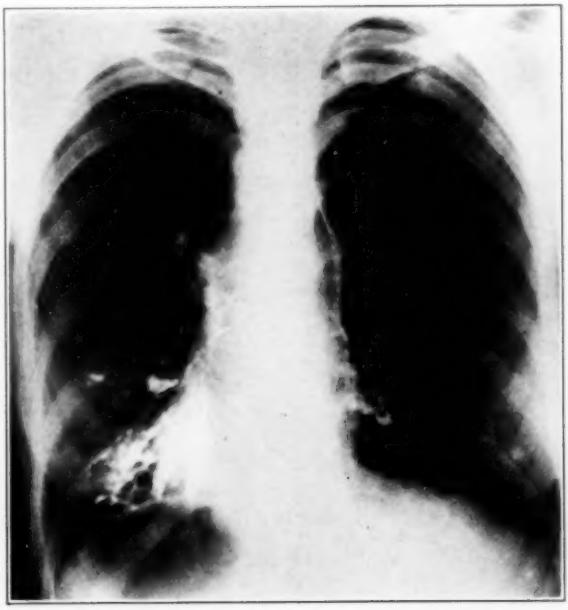

FIG. 2.—**I. Z.** Bronchography left lower lobe. Definite cylindrical and saccular dilatation.

FIG. 3.—I. Z. Bronchography right lower lobe. Immense saccular and cylindrical dilatation.

FIG. 4.—K. W. Bronchography, right lower lobe. Distinct saccular dilatation proximal bronchi. Patient presented no other symptoms aside from chronic bronchitis.

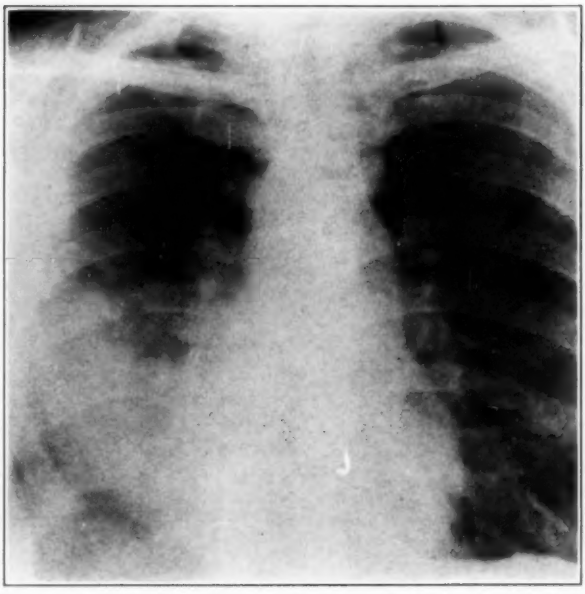

FIG. 5.—Roentgen ray of chest shows marked pleural thickening, left lower. Some hilum increase.

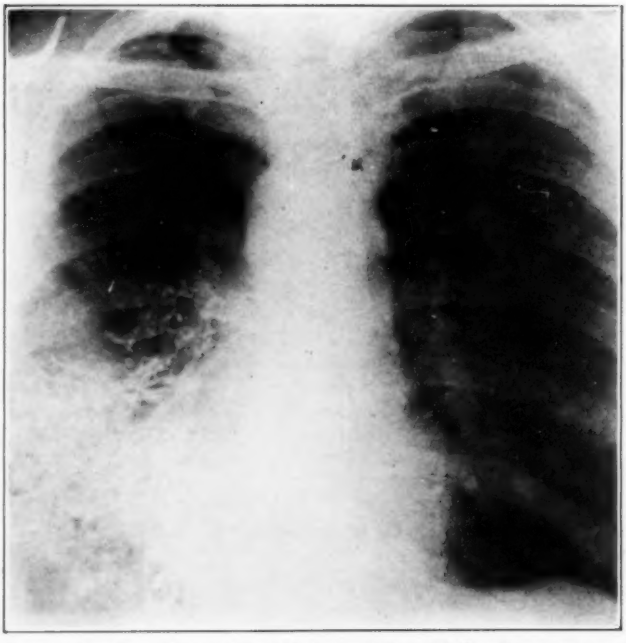

FIG. 6.—O. F.: Bronchography, left lower lobe. Under fluoroscope a definite cylindrical dilatation could be made out. From the Roentgen ray plate, however, it would be impossible to make a diagnosis of bronchiectasis because of the thickened pleura and the presence of the iodized oil in the alveoli.

the lung, the best results are obtained after repeated introductions. We have invariably noted a marked improvement in the patient's

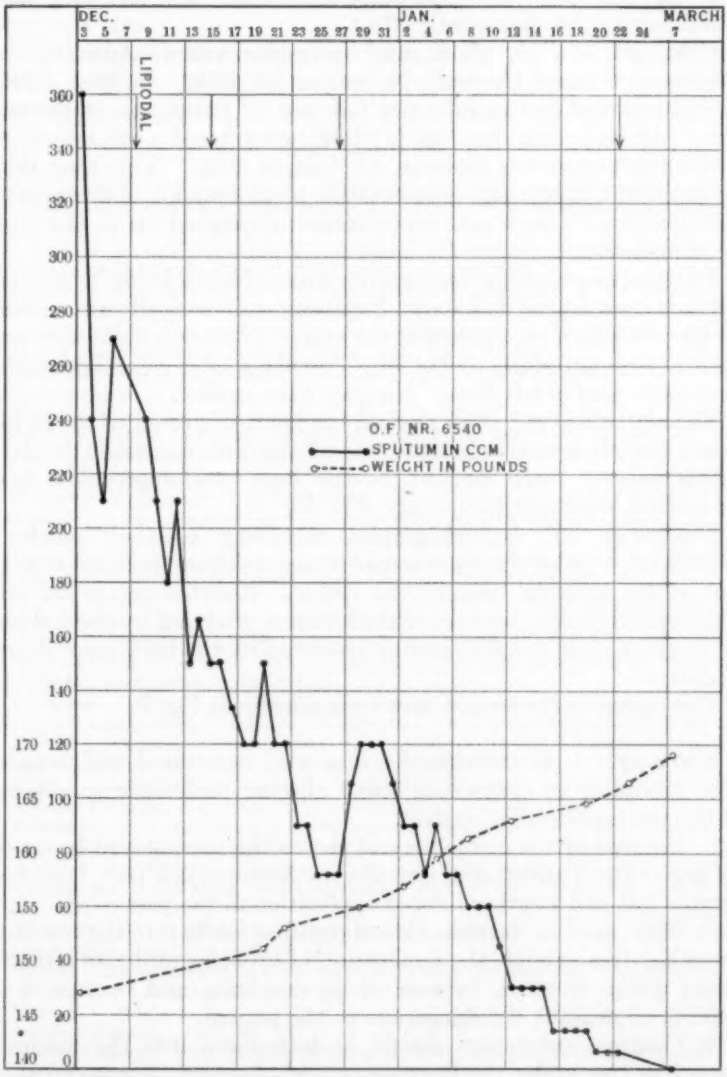

FIG. 7.—O. F. Graphic representation of decrease in sputum and increase in weight following repeated injections of iodized oil into the tracheobronchial tree.

condition following the therapeutic introductions of iodized oil. This improvement is evidenced by decrease in cough and the amount

of sputum, increase in appetite, decrease in the number of organisms in the sputum, gain in weight, loss of tired feeling, ability to sleep well, and the return of temperature to normal. The following case will illustrate the therapeutic effect.

CASE III.—O. F., male, aged forty-nine years. Admitted to Wisconsin General Hospital, November 24, 1926. In May, 1926, the patient had had an influenza followed by pneumonia in the left side. An empyema developed, which necessitated a rib resection. While the wound was draining, he "caught cold." Following this, he coughed a great deal, expectorating large amounts of mucopurulent sputum. Cough and expectoration continued up to the time of admission.

Physical examination was negative except for the following points. The left chest lagged definitely. Expansion was markedly diminished on the left side, most marked at the base. There was dullness below the third rib anteriorly on the left. Breath sounds were diminished over lower part of left lung. No râles were audible.

Stereograms of the chest showed the heart displaced to the right. Below the left second interspace was a flocculent increase in density, which became more marked as the base was approached and assumed a homogeneous quality (Fig. 5).

November 30: Bronchography according to the "passive" technique. Under the fluoroscopic screen a definite saccular dilatation of the terminal bronchi was visible. Roentgenogram did not confirm this finding because of the haziness produced by the iodized oil in the alveoli and the shadow produced by the thickened pleura (Fig. 6).

The course in the case is shown graphically in Fig. 7.

Summary. 1. Bronchography is a well recognized and invaluable procedure in diagnosing many obscure pathologic conditions of the tracheobronchial system.

2. Because of the complexity of the methods employed in introducing contrast substances into the tracheobronchial tree, bronchography has had a rather limited application in the past.

3. The "passive" introduction of contrast media into the tracheobronchial tree extends the application of bronchography to a much larger group of cases, because of its simplicity and because it is neither unpleasant nor dangerous to the patient.

4. Contrast substances should be introduced into the tracheobronchial tree under the fluoroscope and observed fluoroscopically. The "passive" introduction of these substances especially favors fluoroscopic observation.

5. Bronchography is especially indicated in those cases presenting chronic pulmonary symptoms and should not be denied a patient who is suspected of having tuberculosis.

6. In a series of over 700 cases no untoward signs or symptoms have been observed following a bronchography obtained by the "passive" introduction of contrast substances into the tracheobronchial tree.

7. The introduction of iodized oil into the tracheobronchial tree has a decided therapeutic effect in cases of chronic pulmonary infections.

BIBLIOGRAPHY.

Abramowitsch and Tichomirow: Zur Frage der Einführung einer Kontrastsubstanz (Lipiodol) in die Bronchien, Fortschr. a. d. Geb. d. Röntgenstrahlen, 1926, **34**, 22.

Archibald, E., and Brown, A. L.: Dangers of Introducing Iodized Oil into the Tracheobronchial System, J. Am. Med. Assn., 1927, **88**, 1310.

Armand-Delille and Gelston: The Diagnosis of Dilatation of the Bronchi in Children by Means of the Injection of Iodinized Oil, Am. J. Dis. Child., 1924, **28**, 527.

Armand-Delille, Duhamel and Marty: Le diagnostique de dilatation bronchique ches enfants au moyen de Lipiodol, Presse méd., 1924, **32**, 421.

Armand-Delille and Moncrief: The Use of Lipiodol in the Diagnosis of Bronchiectasis, Brit. Med. J., 1924, ii, 7.

Ballon: The Injection of Lipiodol as an Aid in the *X*-ray Diagnosis of Bronchopulmonary Lesions, Including Tuberculosis, Canadian Med. Assn. J., 1925, **15**, 995.

Beck and Sgalitzer: Zur Bronchographie mittels Larynxkatheters, Ztschr. f. Hals u. Ohrenh., 1926, **14**, 8.

Besançon, Weil, Bernard and Azoulay: Le syndrome lipiodo-radiologique de la dilatation des bronches, Bull. et mém. Soc. radiol. méd. de France, 1924, **12**, 32.

Brunfin: Discussion, J. Am. Med. Assn., 1926, **86**, 1804.

Caussade, G., and Tardieu, A.: Les injections trachéales simplifiées par voie sus-glottique (méthode de Mendel), Ann. de méd., 1924, **16**, 167.

Clerf: Bronchoscopic Lung Mapping in Diseases of the Lungs, Surg. Clin. N. America, 1924, **4**, 104.

Clerf: Pneumography, Surg., Gynec. and Obst., 1925, **47**, 722.

Danielson and Manfred: Some Experiences of Bronchography after Injections of Lipiodol, Acta radiol., 1924, **3**, 157.

Dessecker: Beitrag zur pathologischen Physiologie des Schluckaktes and zur Füllung des Bronchialbaumes mit Roentgenbrei, Mitt. a. d. Grenzgb., 1924, **37**, 41.

Dyroff: "Contrastol," ein neues Kontrastmittel für die Darstellung engkalibriger Hohlräume, Deutsch. med. Wchnschr., 1926, **52**, 397.

Egan: "Lipiodol-Lafay," ein Kontrastmittel für die Roentgenuntersuchung der Luftwege, Fortschr. a. d. Geb. d. Röntgenstrahlen, 1925, **33**, 199.

Fiessinger, N., and Lemaire, A.: Des injections lipiodolés comme procédé d, exploration et de traitment des sérites tuberculeuses, Presse méd., 1926, **14**, 209.

Forestier and Leroux: Etude expérimentelle radiologique des injections intratrachéales par l'huile iodee injections lobaire, Bull. et mém. Soc. méd. d. hôp. de Paris, 1923, **47**, 299.

Forestier: Roentgenological Exploration of the Bronchial Tubes with Iodized Oil (Lipiodol), Radiology, 1926, **6**, 303.

Grady: Demonstration of the Bronchial Tree by the Intratracheal Injections of Lipiodol, Am. J. Roentgenol., 1926, **15**, 65.

Grill, C.: Röntgendiagnostische Versuche mit Lipiodol bei Lungentuberkulose, Acta med. Scandin., 1927, **65**, 300.

Guy and Elder: Radiographic Exploration of the Bronchopulmonary System by Means of Lipiodol, Edinburgh Med. J., 1926, **33**, 269.

Hedblom, C. E., and Head, J. R.: On the Use of Lipiodol in Relation to Thoracic Surgery, Ann. Surg., 1927, **85**, 194.

Iglauer: Use of Injected Iodized Oil in Roentgen Ray Diagnosis of Laryngeal, Tracheal and Bronchopulmonary Conditions, J. Am. Med. Assn., 1926, **86**, 1879.

Jackson: Tracheobronchoscopy, Esophagoscopy, Gastrostomy, 1907, p. 69.

Jackson: The Bronchial Tree: Its Study by Insufflation of Opaque Substances in the Living, Am. J. Roentgenol., 1918, **5**, 454.

Jackson, Tucker, Clerf, Lukens and Moore: Bronchoscopy as a Diagnostic Aid to the Thoracic Surgeon, J. Am. Med. Assn., 1925, **84**, 97.

Jacoboeus: On Bronchography in Cases of Purulent Lung Affections, Acta radiol., 1926, **6**, 616.

Killian: Ztschr. f. Ohrenheilk. u. d. Krankh. d. Luftwege, 1908, **55**, 1.

Kovats: Die Röntgendiagnose der Bronchiectasie mittels "Lipiodol-Lafay," Deutsch. med. Wchnschr., 1925, **51**, 653.

Lenk and Hasslinger: Röntgenuntersuchung an normalen und kranken Bronchien nach Fuellung mit Lipiodol, Klin. Wchnschr., 1925, **32**, 1533.

Lenk, Hasslinger and Presser: Diagnose von Erkrankungen der grossen Bronchien, Namentlich Bronchostenosen mittels Kontrastfuellung, Fortschr. a. d. Geb. d. Röntgenstrahlen, 1926, **34**, 117.

Lorey: Ueber den Wert der Kontrastfuellung der Bronchien zur Darstellung der Bronchiektasen, Fortschr. a. d. Geb. d. Röntgenstrahlen, 1925, **33**, 58.

Lorey: Ueber Bronchographie, Verhandlungen der Deutschen Röntgengesellschaft, Fortschr. a. d. Geb. d. Röntgenstrahlen, 1926, **34**, 127.

Lynah and Stewart: Roentgenographic Studies of Bronchiectasis and Lung Abscess after Direct Injections of Bismuth Mixture through the Bronchoscope, Am. J. Roentgenol., 1921, **8**, 49.

Moeller and von Magnus: Investigation of Bronchial Affections by Means of Iodine Preparations (Iodumbrin and Lipiodol), Acta med. Scandin., 1926, **63**, 174.

Nather and Sgalitzer: Zur Technik der Bronchographie, Zentralbl. f. Chir., 1925, **28**, 1534.

Nicaud and Dollfus: Contribution a l'étude du diagnostic des dilatations des bronches par l'exploration radiologique apres lipiodol, Presse méd., 1924, **32**, 817.

Ochsner and Alton: Bronchography Following the "Passive" Introduction of Contrast Media into the Tracheobronchial Tree, Wisconsin Med. J., 1926, **25**, 544.

Pritchard, S., White, B., and Gordon, J. K. M.: Conclusions Regarding Technique, following One Thousand Intratracheal Injections of Iodized Oil in Adults, Radiology, 1927, **8**, 104.

Sergent and Cottenot: L'etude radiologique l'arbre tracheobronchique au moyen des injections intratracheales de lipiodol, Bull. et mém. Soc. méd. d. hôp. de Paris, 1923, **47**, 693.

Sergent and Cottenot: Nécessite des injections intratracheales de lipiodol pour le diagnostic radiologique de la dilatation bronchique, Bull. Acad. de méd., 1924, **91**, 93.

Sergent and Cottenot: Ce que la clinique peut demander aux injections intratrachéals de lipiodol dans le radiodiagnostic des affections de l'appareil respiratoire; difficultés et erreurs d'interpretation, Presse méd., 1925, **33**, 500.

Sgalitzer: Kontrastfuellung des Bronchialbaumes, Arch. f. klin. Chir., 1925, **138**, 197.

Sgalitzer: Voraussetzungen für eine intrabronchiale Einfuehrung von Medikamenten, Arch. f. klin. Chir., 1926, **140**, 305.

Sicard and Forestier: Methode generale d'exploration radiologique par l'huile iodée injections lobaire, Bull. et mém. Soc. méd. d. hôp. de Paris, 1922, **46**, 463.

Sicard and Forestier: Exploration radiologique par l'huile iodée, Presse méd., 1923, **31**, 493.

Sicard and Forestier: L'huile iodée en clinique: Applications thérapeutiques et diagnostiques, Bull. et mém. Soc. méd. d. hôp. de Paris, 1923, **47**, 309.

Sicard and Forestier: L'exploration radiologique des cavités bronchopulmonaires par las injections intratracheales d'huile iodée, J. Med. France, 1924, **13**, 3.

Sicard and Forestier: Exploration with Iodized Oil, Brit. J. Radiol., 1926, **31**, 239.

Singer, J. J.: Bronchography—Injection of Iodized Oil, Forty Per Cent, Arch. Surg., 1927, **14**, 167.

Springer: Verhandlung der Röntgengesellschaft, 1906.

Tagliabue: L'indagine radiologica dell'apparecchio respiratorio con iniezioni intratracheali di lipiodol, Boll. de Soc. med. chirurg., Pavia, 1925, **36**, 575.

Telemann: Verhandlung der Roentgengesellschaft, 1913.

Weingaertner: Physiologische und topographische Studien am Tracheobronchialbaum des lebenden Menschen, Arch. f. Laryngol. u. Rhinol., 1919, **32**, 1.

White, B.: Iodized Oil with Reference to Bronchiectasis, Canadian Med. Assn. J., 1926, **16**, 1443.

Wierig, A.: Die Technik der Bronchographie, Fortschr. a. d. Geb. d. Röntgenstrahlen, 1927, **35**, 787.

Yankhauer: Cited by Lynah and Stewart.

CATARACT AND POSTOPERATIVE TETANY.

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The association of lenticular opacities with muscular spasms has been recognized for many years. In 1872, Logetschnikow,[1] reporting bilateral cataracts in a series of 15 patients with generalized convulsive seizures, the precise nature of which was not stated, expressed the opinion that the cataracts were due not to the convulsions themselves, but to some underlying condition. Schmidt-Rimpler[2] in 1883 again called attention to this coincidence. Of 27 young and middle-aged patients with bilateral cataracts, 4 were found to suffer from "epileptic seizures," while 2 others furnished a history of "hysterical spasms." Thus 6 of the 27 patients were found to be subject to muscular spasms, concerning the exact nature of which, little information is available. In a brief note published subsequently during the same year, this author reported a personal communication from Saemisch[3] to the effect that in middle-aged patients with bilateral cataracts, he had succeeded for many years in eliciting a history of muscular spasms. Teplaschin[4] several years later, in describing 27 cases of bilateral cataracts following an epidemic of ergot poisoning, emphasized their exclusive incidence in the convulsive form of the disease, and a similar observation was reported during the following year by Kortnew.[5] The close resemblance of some forms of ergot poisoning to the picture of tetany (Fuchs,[6] Biedl[7]) suggests that a number of the cases reported by Teplaschin and Kortnew may have been instances of endemic tetany.

An extensive literature has since accumulated, concerning the coincidence of tetany and lenticular opacities, a literature which deals chiefly with the so-called spontaneous or idiopathic form of the disease. Meinert[8] in 1887 reported a case of bilateral lamellar cataracts associated with recurrent attacks of tetany during several pregnancies. A case of bilateral cataract with spontaneous tetany, unassociated with pregnancy was recorded in 1891 by Bernhardt,[9] and further instances of this kind have been described by Logetschnikow,[10] Wettendorfer,[11] Peters,[12] Freund,[13] Sperber,[14] Zirm,[15] Schoenborn,[16] Cantonnet,[17] Hesse and Phleps,[18] von Rutich,[19] Spinnhirny and Reys,[20] and others. Of particular interest is the apparent relationship of the idiopathic tetany of childhood and juvenile cataract. Peters[21] (1901) observed lenticular opacities in 4 cases of tetany in children aged three, four, seven and eight years, and stressed the importance of tetany rather than rickets in the production of these changes. These views were later supported by Hesse and Phleps, who found evidences of tetany in 35 of the 45 patients of various ages with lamellar cataracts studied, while rachitic

changes were found in only 6. Eight patients in the series were under ten years of age, and in 6 of these, evidences of latent tetany were elicited.

Cataracts following parathyreoprival tetany have repeatedly been observed, both experimentally and clinically. Erdheim,[22] in 1906 reported the first experimental cataracts of this variety on record, discovered during the course of chronic tetany in a rat six months after parathyroidectomy. Similar changes were soon observed in parathyroidectomized rats by Pfeiffer and Mayer,[23] Possek,[38] and Adler and Thaler.[24] The last-named authors worked with pregnant parathyroidectomized animals. More recently Hayano[25] studied the eyes of young parathyroidectomized rats, and in almost all cases, observed the appearance of opacities within a few days after operation. These appeared first in the center and soon extended as radiating streaks, to involve the entire lens. Similar observations have been made by Hiroishi[26] who carefully studied the lenses of parathyroidectomized adult rats and observed opacities as early as the sixth day. These changes were the most constant evidences of parathyroid deficiency encountered and occurred in every case in which a complete extirpation had been performed.

In the dog, few observations of this association have been recorded because of the difficulty of maintaining a state of chronic parathyroid deficiency previous to the recent introduction of methods for the control of tetany. Possek,[38] previous to the development of such methods, studied the eyes of sixteen dogs dying in tetany in from twenty-six to one hundred and seventy-two hours after operation, and observed definite changes in the ciliary body, iris and cornea. In addition, a conjunctivitis and inflammation of the lid margins were frequently observed, recalling the changes noted many years previously by Gley and Duvigneau.[27] No mention was made of histologic changes of the lens, however, and careful ophthalmoscopic examination of six animals revealed no striking changes. Edmunds,[28] in 1915, recorded the first actual observation of parathyreoprival cataract in the dog. Bilateral opacities were discovered in an animal kept alive for twenty-three months by the administration of milk and calcium lactate. Death occurred in tetany several days later. In 1923, Luckhardt, and Blumenstock,[29] described bilateral cataracts in dogs kept alive eight months or more by injection of Ringer's solution and the oral administration of calcium lactate. Stimulated by this observation, Dragstedt, Sudan, and Phillips,[30] discovered cataracts in six parathyroidectomized animals in which tetany was being controlled by the administration of calcium lactate or by measures calculated to check intestinal putrefaction. These changes appeared three to six months after extirpation, and led in some cases to the formation of total opacities.

Parathyreoprival cataracts in human beings, following thyroidectomy, have been described in scattered reports beginning in 1888 with that of Landsberg.[31] Recently Greppin[47] collected 18 cases of this variety from German literature and has added one of his own. It is interesting to note that the 18 cases occurred in the total of 33 cases of postthyroidectomy tetany of long standing, which had been reported in German publications from 1880 to 1921—an incidence of over 50 per cent. To Greppin's list may be further added Jeremy's case,[41] (the only one thus far reported in the English literature); 12 cases reported in German since the publication of Greppin's paper, 4 by Knüsel,[48] 2 by Heine,[49] 6 by Kast;[63] and the following 2 cases recently observed in the private practice of Dr. H. M. Richter:

Case Reports. CASE I.—M. C., housewife, aged twenty-three years, was first seen on March 4, 1926. Six months previously (in October, 1925) a radical thyroidectomy had been performed elsewhere for a thyrotoxicosis of four years' standing. Immediately following the operation, there was a complete aphonia, with some inspiratory stridor. During the first few postoperative days, slight sensations of numbness and tingling were experienced in the fingers, and soon after leaving the hospital, the patient began to complain of transient stiffness of the fingers and hands. After about three months her voice gradually returned, but the inspiratory stridor increased in severity. At about this time typical carpopedal spasms, at times associated with generalized spasticity and marked respiratory difficulty, began to occur at intervals of one or two weeks. These attacks lasted for several hours. Several days before the first office visit there had been a particularly severe generalized convulsive seizure, this time with a few moments of unconsciousness. About five weeks previous to this attack, it had been noticed that the scalp hair was becoming thin and short and soon there was a rapidly developing alopecia. At the same time the toe and finger nails became friable, although none was shed.

On examination, the patient was a calm, well-nourished young woman of poor intelligence, with no evidences of thyroid toxicity. There was a marked respiratory stridor, aggravated by physical and mental effort. The scalp hairs were thin, short and scanty, so that in places the scalp was almost bare. Except for a moderate amount of repair work, the teeth showed no abnormalities. The nails appeared normal. Chvostek's sign was markedly positive on both sides. Trousseau's sign was positive bilaterally after less than one minute of compression.

Laryngoscopic examination by Dr. J. Gordon Wilson revealed a bilateral abductor paralysis, the cords being separated by only a small slit.

The blood calcium was 9 mg. per 100 cc. of serum. A basal metabolic rate determined a few days later was +3.

A meat-free diet was prescribed, with 8 drams of calcium lactate and 1 ounce of lactose daily. In two weeks Chvostek's and Trousseau's signs were still strongly positive, and accordingly her calcium and lactose intake was doubled. The blood calcium at this time was 10.5 mg. Several days later there was a most severe generalized convulsive seizure, but during the following month there were no active manifestations of tetany. At the end of this time, during a menstrual period, there was another severe attack, and for several days the usual measures were supplemented by injections of parathormone. It was learned that the patient had not been adhering to her prescribed régime.

At about this juncture, for the first time, she casually complained of slight blurring of vision, which had begun to manifest itself four months previously and was gradually increasing. She was not seen again until June 29, 1927, two months later. During the interval she had faithfully taken 6 drams of calcium lactate and 4 ounces of lactose daily, and had strictly eliminated meat from her diet. Numbness, tingling and stiffness of the extremities had been almost entirely absent. The scalp hair was rapidly growing longer and more abundant. The diminution of vision complained of at her previous visit had, however, steadily progressed and was now particularly marked on the left side. The following eye findings were recorded at this time by Dr. L. Bothman: "Both lenses have diffuse granular opacities throughout, especially dense in the center of the left lens. Under homatropin, 0.6 vision is obtained in the right eye, and only perception of light in the left. Light projection behind the cataract is good and the right disk and fundus are normal by the indirect method. The left fundus is not made out because of dense opacities."

During the subsequent few months the patient was seen at irregular and infrequent intervals. The clinical course during this time was one of gradual general improvement. The dose of calcium lactate was reduced to 1 dram daily, lactose was omitted and proteins were gradually added to her diet. With this régime no active manifestations of tetany, except for an occasional numbness in the fingers, were experienced. The impairment of vision nevertheless slowly progressed.

On January 2, 1927, the following findings were reported: There was a marked inspiratory stridor. The scalp hair was dense and soft, although still rather short. In spite of the absence of manifest symptoms of tetany, Chvostek's sign was very strongly positive. A cathodal opening contraction was obtained with a current of about 2.5 ma. The toe and finger nails showed no definite changes. The cataract on the left had advanced sufficiently for extirpation, but this had been refused, as had operative interference to relieve the respiratory difficulty.

Case II.—G. D., housewife, aged twenty-seven years, was first seen on May 22, 1923, presented a history of thyrotoxicosis of three years' duration, which Roentgen ray therapy had failed to affect materially. On May 24, 1923, a subtotal thyroidectomy was performed by Dr. H. M. Richter. The immediate postoperative course was satisfactory, but an examination on July 11, 1923 revealed definite evidences of residual toxicity. In March, 1924, the patient became pregnant, and a normal child was born in October, 1924. During this pregnancy, toxic manifestations had almost entirely subsided, but several months later, they recurred. On April 10, 1925, the patient was reoperated upon, a moderate amount of residual thyroid tissue being removed, with prompt and lasting subsidence of toxicity. Two weeks after this operation, however, she began to complain of numbness and tingling in the fingers and toes, and of a sensation of stiffness about the lips. On examination, Chvostek's and Trousseau's signs, which had been negative before the operation, were found to have become strongly positive. During the following week, on a diet restricted in proteins, some numbness and tingling persisted, and there were occasional carpopedal spasms. On calcium lactate, 1 ounce, and a meat-free diet, active manifestations of tetany were controlled, except for slight numbness and tingling. Chvostek's and Trousseau's signs remained positive. However, the régime prescribed was not strictly adhered to, calcium lactate and lactose being frequently omitted for weeks or even months.

During the first eighteen postoperative months, carpopedal spasms still occurred during such periods. But during the following six months, complete omission of calcium and lactose were attended only by slight tingling and numbness, always promptly relieved by a return to a strict régime.

Thus the course of the parathyroid deficiency itself was one of distinct gradual improvement. When the patient was seen on April 25, 1927, no calcium or lactose had been taken for some weeks. Chvostek's sign was only feebly positive Erb's sign was negative, and there were no subjective symptoms of tetany.

CASES OF CATARACT DEVELOPING AFTER THYROIDECTOMY.

Author.	Year of publication.	Age of patient.	Sex.	Time of onset after operation.*	Hair changes.†	Nail changes.†
Landsberg	1888	25	F.	1 year	O	O
von Eiselsberg	1892	24	M.	Cataract removed after 1 year	+	+
Hoffman	1897	36	F.	6 months	+	+
Schiller	1899	36	F.	6 months	+	+
Westphal	1901	Not stated	F.	4½ years	O	O
Wagenman	1902	40	F.	?	O	O
Koenigstein	1907	?	F.	8 years	O	O
Possek	1907	29	F.	4 months	+	+
Purtscher	1909	26	F.	Several days (?)	+	+
Vogt	1911	39	F.	Observed 20 years after operation. Time of onset not known	O	O
Jeremy	1919	50	F.	3 months	O	O
Hammerschmidt	1919	24	M.	22 months	O	O
Jaeger	1920	41	F.	6 months	O	O
		42	F.	5 years	O	O
Pamperl	1921	32	F.	8 months	O	O
Eiselsberg	1921	47	F.	11 years	O	O
		39	F.	7 years	O	O
		35	F.	1 year	O	O
Sidler-Huguenin	1922	40	F.	3 months	O	O
Greppin	1923	42	F.	4 to 5 months	+	O
Knuesel	1924	23	F.	7 years	O	O
		31	F.	Positive slitlamp findings. No visual disturbance	O	O
		34	F.	20 months	O	O
		32	F.	8 months	O	O
Heine	1925	39	F.	20 years (?)	O	O
		31	F.	Several months	O	O
		28	F.	2 years	+	O
		38	F.	13 years	O	O
Kast	1926	48	F.	3 years	O	O
		42	F.	2 years	+	O
		31	M.	4 months	O	O
		42	M.	10 years	+	+
Present cases	1927	23	F.	2 months	+	+ (?)
		27	F.	1 year	O	O

* In most instances, the period recorded represents the time of onset of definite visual disturbance referable to the cataracts.

† The negative sign usually indicates that no mention has been made of the changes in question. In a few instances their absence is explicitly stated.

In April, 1926, about a year after her second operation, the patient began to complain of blurring of vision in both eyes. This was slowly progressive. On April 19, 1926, fourteen months postoperatively, an ophthalmological

examination by Dr. J. Lebensohn revealed bilateral perinuclear opacities, more extensive on the right side. The visual disturbance gradually increased and continued to increase in spite of the definite diminution in the degree of parathyroid deficiency. On April 19, 1927, an examination by Dr. Lebensohn revealed an increase in the opacities in both lenses. The condition was now accompanied by lenticular swelling, which had induced myopia for distance. On May 13, 1927, Chvostek's and Trousseau's signs were again definitely positive. The patient had been freely breaking her régime. During the following month, on small amounts of calcium lactate and a strictly meat-free diet, Chvostek's and Trousseau's signs remained negative. No definite change in vision occurred in this interval. At this time (June 13, 1927) the patient was put on parathormone, 1.5 cc. every other day. The meat-free diet was continued. Under these conditions, she has remained free of all evidences of increased neuromuscular excitability. Dr. Lebensohn, however, reports that the lens changes continue to advance.

Discussion. It will be noted that 30 of the 34 cases tabulated, occurred in females, a preponderance which is probably due partly to the higher incidence of goiter and hence of thyroidectomy in women, and partly to the higher susceptibility of this sex to tetany, particularly during menstruation, pregnancy and lactation. As a rule, the cataracts were discovered within the first two years after operation. In Purtscher's case,[39] although rapid diminution of vision occurred several days postoperatively, no statement is made as to the observation of lens changes at this time, although seven months later there were extensive bilateral cataracts. It seems unlikely that the early diminution of vision was due to such changes, although Freund has described 2 cases of endemic tetany in which lenticular opacities appeared to develop within several days after the onset of manifest symptoms and a similarly rapid appearance of such lesions has been observed by Hayano and Hiroishi in rats. On the other hand, it is noteworthy that in many of the cases tabulated, the cataracts were not discovered for a period of years following operation. In Vogt's case,[40] for instance, lens changes were first recognized after twenty years had elasped. Definite carpopedal spasms had occurred throughout this period. One suspects that the relationship of opacities discovered after such an interval, to a thyroidectomy performed years previously, has frequently been overlooked. It is furthermore quite possible that a systematic ophthalmologic examination in all cases of postoperative tetany would reveal a much earlier appearance, and higher incidence of such alterations. Knüsel[48] has recently called particular attention to the value of the slit lamp for this purpose and has pointed out that characteristic lesions may be demonstrated by its use even in the absence of visual disturbances, a fact illustrated by this author's first case in the table.

The precise nature of the lens changes occurring in tetany will not be discussed here. The cataracts which have been observed have practically always been bilateral and in the great majority

of cases have been of the lamellar or perinuclear variety, becoming total cataracts similar to those arising from other causes, when the process has reached maturity. Anatomic studies of such opacities have been recorded by Peters in cases of endemic tetany, and by Possek in the experimental tetany of rats.

These lenticular lesions together with changes affecting various other ectodermal derivatives constitute the so-called "trophic" disturbances of chronic tetany. The hair changes and perhaps the friability of the nails described in the first case are to be regarded as manifestations of this character. The hair changes associated with tetany may range from a simple thinning of the scalp hairs to a complete generalized alopecia. In Adler and Thaler's experiments on pregnant rats, an alopecia regularly preceded the active manifestations of tetany and was regarded as a reliable indication of the approach of spastic and convulsive phenomena. In the present case, the regrowth of hair served as a striking index of the patient's clinical improvement. The nail changes taking place in chronic tetany were first described by Herard[50] (1843) in the severe endemic form of the disease and have been noted in various forms of tetany, clinical and experimental. All degrees of derangement, from slightly increased friability and grooving, to extensive necrosis with repeated complete shedding and regrowth have been observed. No tooth changes have been described in human postoperative tetany, and none was found in either of the present cases. However, characteristic alterations of dentition and enamel defects have been noted in the tetany of children, and Erdheim and others have described extensive enamel defects in rats.

Both hair and nail changes were found in 7 of the postoperative cases here tabulated, while alopecia alone occurred in 2.

As to the etiology of the cataracts of tetany, little information is available. While, in a great majority of the cases recorded, actual generalized convulsions have occurred, such phenomena cannot be regarded as essential to the development of the cataracts. No mention of epileptiform seizures is made in several of the postoperative cases tabulated and none took place in the second case here reported. Hiroishi pointed out that opacities were found in some of his rats in the absence of clonic spasms or generalized convulsions. Little is known regarding the immediate pathogenesis of these lesions. Peters,[51] who has written extensively on the subject, early attributed their development to a ciliary muscle spasm, This theory was soon abandoned and the notion substituted for it that the lens changes were the result of the selective action of toxins on the epithelium of the ciliary body, producing in this way an increase in the protein and inorganic salt content of the aqueous humor, to which the lens alterations were considered directly due. Support for these views was sought in studies made upon experimentally produced naphthalin cataracts in rabbits, which are said

to resemble structurally the cataracts of tetany. (Peters and Possek). Peters' conclusions have been vigorously opposed by Leber,[52] Possek[38] and others, the details of which controversy need not be considered here. The opinion is repeatedly expressed in some of the older as well as in the more recent literature (*e. g.* Luckhardt and Dragstedt) that the lenticular damage is produced by the action of toxins upon the lens epithelium, but the acceptance of these views must be deferred until more precise information has become available regarding the nature of these substances. Stoelzner,[53] in a series of experiments, sought to enlist the occurrence of tetany cataract to the support of his calcium poisoning theory of tetany. His experiments were followed by those of Nelson.[54] The opacities produced by these authors by the immersion of extirpated lenses in inorganic solutions, developed most readily in the presence of calcium salts, in all probability because of the hygroscopic properties of these substances. Burge[55, 56] demonstrated an increase in the calcium content of senile cataractous lenses from the almost negligible amount found in normal lenses to 12.5 per cent of the total ash. A smaller increase was found in the magnesium and sodium content. On the basis of these facts, he immersed isolated lenses in solutions of calcium chlorid, sodium chlorid, and potassium chlorid. Opacities were readily produced by solutions considerably stronger than might possibly be encountered in living animals. It was found, however, that opacities could be produced by considerably weaker solutions of the same salts if the lenses were subsequently exposed to ultraviolet radiation. The possible relationship of these facts to the occurrence of cataracts in tetany is not discussed. Recently Greenwald[57] has presented evidence to the effect that in the absence of the parathyroids there is an extensive deposition of calcium, probably in the form of calcium phosphate, in the tissues, and has suggested the possibility that "the cataracts so frequently observed in parathyroidectomized dogs and in cases of tetany in man may be due to a deposition of calcium phosphate in the lens."*

It is noteworthy that in the first case here reported the lenticular changes were progressive in spite of the general improvement, as shown by the regrowth of hair and by the reduction in the amount of calcium required to prevent the development of active manifestations. One is inclined to infer either that these progressive changes constituted the gradually maturing end results of active lenticular injury earlier in the disease, or that the lens epithelium was more sensitive to the injurious influences at work, than the hair. That

* Since this article was sent to press, Eiseman and Luckhardt[44] have reported an investigation of the factors responsible for cataracts in tetany. Artificially induced convulsions, depression of the blood calcium by the injection of oxalates and phosphates, elevation of the blood phosphates and injections of calcium lactate and sodium bicarbonate all failed to produce lens alterations.

the lens is not invariably more sensitive than other ectodermal derivatives is demonstrated by the fact that both clinically and experimentally hair and nail changes have been observed in the absence of manifest lenticular degeneration (Hoffman,[58] Danielson,[59] Stern,[60] Nicolaysen[61]). No adequate explanation is at present available for the damage of particular derivatives in certain cases, nor are the factors determining the development of any of these disturbances in a particular case yet understood. Our experience does not support the view expressed in the literature that their incidence is directly proportional to the duration and severity of the tetany. We have had occasion to observe one case in which the neuromuscular manifestations exceeded, and several in which such symptoms equalled in the duration and severity, those occurring in the present cases, none of which have been associated with "trophic" disturbances.

Whatever the factors responsible for these changes may be, it is to be emphasized here that the continued development of lenticular opacities in the presence of relatively mild degrees of parathyroid deficiency demonstrates the necessity for the prompt recognition and accurate control of all degrees of postoperative tetany, including the latent form, if such unfortunate consequences are to be prevented. Any adequate scheme of management must be designed to combat the "trophic" as well as the neuromuscular manifestations of the condition. We have heretofore been content to attempt to secure complete control of all latent and active evidences of nervous and neuromuscular disturbance. The measures employed have consisted essentially in the administration of adequate amounts of calcium and in a restriction of the protein intake, the injection of parathormone being resorted to only in the presence of acute symptoms, or when, for various reasons, the oral administration of calcium has been made difficult or impossible. Unfortunately, in neither of the cases here reported, was the coöperation of the patient sufficient to permit such measures to be adequately carried out.

The continued development of the cataracts in the second case in spite of only mild evidences of parathyroid deficiency, led us to suspect that the measures being employed, while they might, if properly enforced, abolish the outstanding manifestations of tetany, were not equivalent to a true replacement therapy. We, therefore, decided to control this patient with adequate doses of parathormone. It was hoped that in this way the progress of the cataracts might be checked; it was furthermore thought possible that if the opacities were indeed due at least in part to a deposition of calcium salts within the lens, some improvement might be brought about by the demobilization of such deposits. ("Parathyroid hormone" has been used on the treatment of senile cataract by Kerr, Hosford, and Shepardson.[62]) The neuromuscular manifestations of tetany were readily controlled by small doses of parathormone. Unfortunately,

however, up to the time of the present writing, eight weeks since the institution of this régime, the cataracts have continued to advance.

Summary. Two cases of bilateral cataract developing in the course of postoperative tetany are recorded. In 1 case there was a marked alopecia of the scalp hair. Attention is called to the relatively frequent occurrence of lens, hair, and nail changes, not only in postoperative tetany, but also in the so-called spontaneous forms of the disease. Thirty-four cases of postoperative tetany cataract collected from the literature are briefly tabulated. Only 4 of these occurred in males. The opacities were discovered in most instances within two years following operation. Hair and nail changes occurred in 7 cases in the series, hair changes alone, in 2. The theories relating to the pathogenesis of these changes are briefly discussed. The necessity for prompt and adequate control of postoperative tetany to avoid such complications is emphasized. In 1 case, the administration of parathormone has failed to arrest the progress of the cataracts.

BIBLIOGRAPHY.

1. Logestschnikow, S.: Zur Frage über den Zusammenhang des grauen Staares mit der Enkrankung des Nervensystems, Klin Monatsbl. f. Augenh., 1872, **10**, 351.
2. Schmidt-Rimpler, H.: Zur Aetiologie der Kataract Entwickelung im mittleren Lebensalter, Klin. Monatsbl. f. Augenh., 1883, **21**, 181.
3. Saemisch: Quoted by Schmidt-Rimpler, Klin. Monatsbl. f. Augenh., 1883, **21**, 246.
4. Tepljaschin, A.: Katarakt bei Ergotismus, Jahres b. über die ges. Ophth., 1889, **20**, 275.
5. Kortnew, A.: Jahresb. über die ges. Ophth., 1892, **23**, 518.
6. Fuchs, A.: Analogien im Krankheitsbilds des Ergotismus und der Tetanie, Wien. klin. Wchnschr., 1911, **24**, 1073.
7. Biedl, A.: Innere Sekretion, Urban & Schwazenberg, Berlin, 1913, p. 96.
8. Meinert: Tetanie in der Schwangerschaft, Arch. f. Gynäkol., 1887, **30**, 444.
9. Bernardt, M.: Ueber das Vorkommen der idiopathischer Tetanie in Berlin, Berl. klin. Wchnschr., 1891, **28**, 633.
10. Logetschnikow, S.: Eine Staarextraction bei Morbus Basedowi, Klin. Monatsbl. f. Augenh., 1891, **29**, 661.
11. Wettendorfer, F.: Ein Beitrag zur Aetiologie des juvenilen Totalstaares, Wien. med. Wchnschr., 1897, **47**, 527.
12. Peters, A.: Tetanie und Staarbildung, Friedrich Cohen, Bonn, 1898.
13. Freund, H.: Tetanie als Ursache der Staarbildung. Wien. med. Wchnschr., 1904, **54**, 405.
14. Sperber, E.: Zur Tetanie Cataract, Arch. f. Augenh., 1906, **54**, 386.
15. Zirm, E.: Zur Tetanie—Cataract, Arch. f. Augenh., 1905, **52**, 183.
16. Schoenborn, S.: Klinisches zur menschlichen Tetanie im Anschuss an 41 Fälle, Deutsch. Ztschr. f. Nervenh., 1910, **40**, 319.
17. Cantonnet, M. A.: Cataractes chez une malade atteinte de myxoedeme et de tetanie, Rev. Neurol., 1910, **18**, No. 1, 240.
18. Hesse, R., and Phleps, E.: Shichtstaar und Tetany, Ztschr. f. Augenh., 1913, **29**, 238.
19. von Rutich, E.: Pupillenstarre, Areflexie, und Katarakt bei Tetanie, Deutsche. med. Wchnschr., 1925, **51**, 2079.
20. Spinnhirny, C., and Reys, L.: Cataracte et Tetanie chez l'adulte, Rev. d'otoneuro-oculistique, 1925, **3**, 299.
21. Peters, A.: Weiteres über Tetanie und Staarbildung, Ztschr. f. Augenh, 1901, **5**, 89.
22. Erdheim, J.: Tetania parathyreopriva, Mitt. a. d. Grenzge. d. Med. bu. Chir., 1906, **16**, 632.

23. Pfeiffer, H., and Mayer, O.: Experimentelle Beiträge zur Kenntnis der Epithelkörperchenfunktion, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1907, **18**, 377.
24. Adler, L., and Thaler, H.: Experimentelle und klinische Studien über die Graviditätstetanie, Ztschr. f. Geburtshülfe u. Gynekol., 1908, **62**, 194.
25. Hayano, R.: Quoted by Biedl. 1922 (original article in Japanese).
26. Hiroishi, H.: Ueber die parathyreoprive Kataraktbildung bei Ratten, Arch. f. Ophth., 1924, **113**, 381.
27. Gley, E., and Duvigneau, A.: Contribution à l'étude des troubles trophiques chez des chiens thyréotomisés—alterations oculaires chez ces animaux, Arch. d. Physiol., 1894, **26**, 101.
28. Edmunds, W.: Double Cataract following Experimental Total Thyroidectomy in a Dog, Proc. Roy. Soc. Med. 9, Sect. on Ophthal., 1915, p. 53.
29. Luckhardt, A. B., and Blumenstock, J.: Additional Observations on Completely Thyroparathyroidectomized Dogs, Am. J. Physiol., 1923, **63**, 409.
30. Dragstedt, L. R., Sudan, A. C., and Phillips, K.: Studies on the Pathogenesis of Tetany IV. The Tetany of Oestrus, Pregnancy, and Lactation, Am. J. Physiol., 1924, **69**, 477.
31. Landsberg, M.: Zur Aetiologie der Kataraktbildung, Zentralbl. f. prakt. Augenh., 1888, **12**, 39.
32. von Eiselsberg, A.: Weitere Beiträge zur Lehre von den Folgezustanden der Kropfoperation, Beitr. z. Chir. Ferdinand Enke, Stuttgart, 1892, p. 371.
33. Hoffman, J.: Weiterer Beitrag zur Lehre von der Tetanie, Berl. klin. Wchnschr., 1901, **38**, 849.
34. Schiller, A.: Ueber die Kropfoperationen an der Heidelberger Klinik in den Jahren, 1888–1898, Beitr. z. klin. Chir., 1899, **24**, 535.
35. Westphal, A.: Weiterer Beitrag zur Lehre von der Tetanie, Berl. klin. Wchnschr., 1901, **38**, 489.
36. Wagenman: Quoted by Greppin.
37. Koenigstein: Sitzungsberichte Ophthalmologische Gesellschaft in Wien. klin. Monatsbl. f. Augenh., 1907, **45**, 268.
38. Possek, R.: Schildrüse und Auge. Klin. Monatsbl. f. Augenh., 1907, **45**, Beilageheft, p. 1.
39. Purtscher, O.: Ueber Staarbildung nach Kropfoperation, Zentralbl. f. prakt. Augenh., 1909, **33**, 97.
40. Vogt, A.: Tetanie nach Strumektomie, Correspondenzbl. f. Schweiz. Aerzte, 1911, **41**, 695.
41. Jeremy, H. R.: Cataract following Thyroidectomy, Brit. J. Ophth., 1919, **3**, 315.
42. Hammerschmidt: Diss. Tubingen, 1919 (quoted by Greppin).
43. Jaeger, Hans: Erfahrungen über den Wert der Epithelkörperüberpflanzung bei postoperativer Tetanie, Zentralbl. f. Chir., 1920, **47**, 565.
44. Pamperl, R.: Zur Entstehung und Behandlung der postoperativen Tetanie, Deutsch. Ztschr. f. Chir., 1921, **161**, 258.
45. von Eiselsberg, A.: Zur Behandlung der Tetania parathyreopriva, Arch. f. klin. Chir., 1921, **118**, 387.
46. Sidler-Huguenin: Stauungspapille bei Tetanie, Arch. f. Ophth., 1922, **107**, 1.
47. Greppin, M.: Ueber einen Fall von parathyreopriver Tetanie mit Kataraktbildung und Epithelkörperchen Transplantation, Inaug. Diss. Basel, 1923, and Schweiz. med. Wchnschr., 1922, **52**, 1260.
48. Knüsel, O.: Das Spaltlampenbild der postoperativen Tetaniekatarakt, Arch. f. Ophth., 1924, **114**, 636.
49. Heine, L.: Ueber Tetanie und Myotonie Katarakt., Ztschr. f. Augenh., 1925, **55**, 1.
50. Quoted by Barker, L. F.: Endocrinology and Metabolism, D. Appelton & Co., London, 1922, **1**, 614.
51. Peters, A.: Weitere Beiträge zur Pathologie der Linse, Klinischer u. Anatomischer. Teil. klin. Monatsbl. f. Augenh., 1901, **39**, 351.
52. Leber, T.: Zur Pathogenese der Katarakt, Klin. Monatsbl. f. Augenh., 1905, **43**, 324.
53. Stoelzner, W.: Ueber Tetaniekatarakt, Ztschr. f. Kinderh., 1913, **7**, 425.
54. Nelson, F.: Experimentelle Beiträge zur Frage des Kalkstoffwechsels bei der Tetaniekatarakt, Klin. Monatsble. f. Augenh., 1923, **70**, 641.
55. Burge, W. E.: Analyses of the Ash of the Normal and the Cataractous Lens, Arch. Ophth., 1909, **38**, 435.
56. Burge, W. E.: The Production of Cataract, Arch. Ophth., 1918, **47**, 12.

57. Greenwald, I.: The Effect of the Administration of Calcium Salts and of Sodium Phosphate upon the Calcium and Phosphorus Metabolism of Parathyroidectomized Dogs, with a Consideration of the Nature of the Calcium Compounds of the Blood, and their Relation to the Pathogenesis of Tetany, Am. J. Physiol., 1926, **67**, 1.
58. Hoffman: Zur Lehre von der Tetanie, Deutsch. Arch. f. klin. Med., 1888, **43**, 53.
59. Danielson, W.: Erfolgreiche Epithelkörpertransplantation bei Tetanie parathyropriva, Beitr. z. klin. Chir., 1910, **66**, 85.
60. Stern, A.: Demonstration eines Falles von Tetania strumapriva, Berl. klin. Wchnschr., 1914, **51**, 662.
61. Nicolaysen, J.: Transplantation von Parathyroidea bei postoperativer Tetanie, Zentralbl. f. Chir., 1915, **42**, 30.
62. Kerr, W. J., Hosford, G. N., Shepardson, H. C.: Treatment of Senile Cararact with Thyroid Extract, Endocrinology, 1926, **10**, 126.
63. Kast, H.: Katarakt nach Strumektomie, Ztschr. f. Augenh., 1926, **59**, 357.
64. Eiseman, C., and Luckhardt, A. B.: Mechanism of Cataract Formation in Thyroparathyroidectomized Dogs, Proc. Soc. of Exp. Biol. and Med., 1927, **25**, 6.

SYNTHALIN IN THE TREATMENT OF DIABETES MELLITUS.*

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EUROPEAN literature contains a number of reports on this new therapeutic agent, synthalin. The possibilities of its use in the treatment of diabetes were first brought to the notice of the profession by Frank, Nothmann and Wagner[1] in November, 1926. The experimental period has been reviewed by Frank.[2] Synthalin is a guanidin compound in which, Frank states, the methyl side chains are lengthened. It is to this that the greater blood-sugar lowering effect and lessened toxicity are attributed.

Frank, Nothmann and Wagner report that the blood sugar was lowered in normal and diabetic animals, that orally it was nearly as effective as when given subcutaneously, that in a study of 70 patients, the action was slower than that of insulin and that the patients continued to benefit throughout the day which followed two days of treatment. They also found a reduction of ketosuria with experimental evidence that glycogen was stored. The toxic symptoms, anorexia, abdominal distress, nausea and diarrhea could be prevented by omitting all synthalin every third day. Furthermore they found that its use permitted an increase of 40 to 50 gm. of carbohydrate daily, not otherwise tolerated without increasing the insulin, that in severe diabetes it could not replace insulin but was an effective supplement and that pruritus, infection and gangrene were alleviated.

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Morawitz,[3] with 30 diabetics suitable for study, confirmed the earlier work and pointed out that the distaste for fat was a prominent symptom of overdosage and that relief was obtained and a greater synthalin dosage permitted by giving 0.5 gm. of decholin (sodium dehydrocholate) with each dose of synthalin. Later, benefit was obtained with free dehydrocholic acid (0.3 gm.). The beneficial action of the bile salts and the suspicion that liver damage might ensue from prolonged administration of synthalin were first reported by Adler.[4] One patient, an alcoholic with diabetes and possible liver dysfunction, is reported by Morawitz to have had pain over the liver and icterus beginning after two and one-third months of treatment with synthalin. Adler quotes Holzweissig's patient, in whom icterus followed a sudden gastrointestinal upset after the prolonged use of synthalin. One of the cases reported by Rabinowitch[5] gave evidence of a disturbed liver function. Lorenzen[6] discourages clinical use of synthalin. Richter,[2] Umber,[2] Strauss,[2] Carrasco,[7] De Jong,[8] Priesel and Wagner,[9] and others have contributed to the literature on the subject.

The material chosen for this study consists of 3 patients recently admitted and studied on Dr. McCrae's service, and 4 private patients with a longstanding, controlled diabetes. Myrtillin, recently reported on by Allen and Wagner, has been given to 4 of this group with benefit to 3. However, the variations in the potency of this product, up to this time, make it advisable to delay a comparative report.

Qualitative tests for sugar were done on the 7 A.M., 11 A.M., and 4 P.M. urine specimens in all but 1 case (L. M.), in which tests were done on the 7 A.M. and 4 P.M. collections. Blood analyses were done at convenient intervals. The Lewis modification of the Benedict method was utilized to determine the plasma sugar in the case of the private patients. The Folin-Wu method was used in the hospital.

The synthalin, in doses of 10 mg. and higher, was given orally immediately before meals.

Case Reports.—Mrs. M. K., white, aged sixty-four years; height, 5 feet 3 inches; weight, 96 pounds, was admitted to Dr. McCrae's service June 25. Her chief complaints were: Loss of weight (90 pounds in the past year), loss of appetite, dryness of the mouth, constipation, pains in the legs and shortness of breath. Each member of her mother's family suffered from tuberculosis. One sister has diabetes. Her past illnesses were: Smallpox, pneumonia, typhoid, asthma and an operation for retroverted uterus at twenty-three years of age. She had one pregnancy and no miscarriages. The present illness dates from July, 1926, when the diabetes was first discovered. The complaints were general malaise and loss of weight. She attended the outpatient department irregularly and was not faithful with her diet.

The positive physical findings were: Emaciation, dryness of the skin decreased intra-ocular tension, dry tongue, acetone odor to the breath, area of fibrosis in apex of left lung, blood pressure, 115 systolic, and 70 diastolic,

varicosities of veins of both legs and no pulsation in the dorsalis pedis artery (bilateral). The laboratory analyses revealed a negative Wassermann test, normal blood count with positive reactions for sugar, acetone and diacetic acid in the urine. The specific gravity was 1032 and there was no albumin. Unfortunately the blood analysis was not done until the third day. In view of the existing acidosis (mild) a diet, liberal in carbohydrate, was prescribed and insulin begun. Fluids were forced and an enema given. The diabetes was controlled with a diet, 70 gm. protein, 80 gm. carbohydrate and 2000 calories, and 54 units of insulin daily. Synthalin was begun July 8, and through a misunderstanding the insulin was discontinued. Glycosuria returned in the 7 A.M. urine on the following day. With one exception succeeding tests revealed no sugar. The plasma sugar was slightly elevated. Synthalin was stopped July 15. Sugar appeared in one subsequent specimen only. The blood sugar, the second day free from synthalin, was normal. She was discharged on July 16, before our study was completed. One week later heavy glycosuria had returned. There was no reason to believe that she was not adhering to her diet.

Comment. The reappearance of glycosuria on the second day of synthalin treatment, the return to normal, the recurrence of heavy glycosuria following the discontinuance of synthalin tend to strengthen the possibility that here synthalin made possible the reduction in the number of doses and the discontinuance of insulin. Glycosuria returned July 15, the day succeeding the onset of symptoms of synthalin overdosage.

MRS. M. K., AGE, SIXTY-FOUR YEARS; HEIGHT, 5 FEET 3 INCHES; WEIGHT, 96 POUNDS.

Date.	Diet. P.	F.	C.	Cal.	Insulin, units.	Synthalin, mg.	Urine, sugar.	Blood sugar.	Remarks.
June 25	26	33	40	561	30 (1 dose)	— — —	H	....	Admitted in P. M., heavy acetonuria.
26	80	100	120	1700	30 (3 doses)	— — —	H H H	....	Moderate acetonuria.
27	80	100	120	1700	30 (3 doses)	— — —	M M M	218 mg.	
28	70	155	80	2000	55 (3 doses)	— — —	M M O		
29	70	155	80	2000	55 (3 doses)	— — —	O tr. O		
30	70	155	80	2000	55 (3 doses)	— — —	O O O	....	Weight 100 pounds.
July 1	70	155	80	2000	55 (3 doses)	— — —	O tr. O		
2	70	155	80	2000	54 (3 doses)	— — —	O O O	93 mg.	
3	70	155	80	2000	54 (3 doses)	— — —	O O O	132 mg.	Weight 102 pounds.
4	70	155	80	2000	54 (3 doses)	— — —	O O O		
5	70	155	80	2000	54 (3 doses)	— — —	O O O		
6	70	155	80	2000	54 (3 doses)	— — —	O O O		
7	70	155	80	2000	52 (3 doses)	— — —	O O O	....	Weight 106 pounds.
8	70	155	80	2000	O	10 10 10	O O O		
9	70	155	80	2000	O	10 10 10	tr. O O		
10	70	155	80	2000	O	10 10 25	O O O		
11	70	155	80	2000	O	— — —	O O O		
12	70	155	80	2000	O	10 10 25	O O O	155 mg.	
13	70	155	80	2000	O	10 10 25	O O O	160 mg.	
14	70	155	80	2000	O	10 10 —	O O O	....	Loss of appetite.
15	70	155	80	2000	O	— — —	O tr. O		
16	70	155	80	2000	O	— — —	O O O	126 mg.	Discharged.

H = heavy M = moderate tr. = trace.

Mr. H. W., white, age, fifty-seven years, height, 5 feet 11 inches; weight, 147 pounds; gives a history of diabetes since 1912, when glycosuria was found in a routine examination following a minor injury. In 1922 he was markedly undernourished and when treated at the Physiatric Institute an advanced acidosis was found. The undernutrition régime was begun until a sufficient supply of insulin was available. The diabetes was kept under fair control with a weighed diet and a large insulin dosage. When seen in September,

1926, 56 units were required daily, with a diet of 100 gm. carbohydrate, 100 gm. protein and 2200 calories to maintain normal plasma sugar figures. Moderate undernutrition, chronic pharyngitis, diseased tonsils and an area of fibrosis in the apex of the right lung were the positive findings on physical examination. The past illnesses were: Scarlet fever, pharyngitis, suspected chronic appendicitis (1900) and sciatica (1907). Since the onset of the diabetes, neuritis (right leg) and "head colds" have been frequent. During the past year the insulin requirement remained fairly constant with the exception of a period of four months. During this time myrtillin was used and the insulin dosage was as low as 24 units daily.

Synthalin was first given July 19, 1927. Prior to this date it was almost impossible to prevent abnormal blood sugar percentages and glycosuria.

Comment. The rapid reduction of insulin, the symptoms of hypoglycemia on a lower dosage, the elimination of one dose, the increased need for insulin after the onset of symptoms of synthalin overdosage (July 27), and the decrease of insulin following the alleviation of the last mentioned, are worthy of note. Synthalin was stopped August 31. The insulin dosage was increased rapidly to the present requirement, 42 units (11 units below the pre-synthalin requirement).

MR. H. W., AGE, FIFTY-SEVEN YEARS; HEIGHT, 5 FEET 11 INCHES; WEIGHT, 147 POUNDS.

Date.	Diet. P.	F.	C.	Cal.	Insulin, units.	Synthalin, mg.	Urine, sugar.	Blood sugar, CO_2; time.	Remarks.
July 13	100	168	115	2375	51 (4 doses)	— — —	O O O	....	Weight 147 pounds.
14	100	168	115	2375	55 (4 doses)	— — —	O tr. O		
15	100	168	115	2375	57 (4 doses)	— — —	tr. tr. tr.		
16	100	168	115	2375	53 (4 doses)	— — —	tr. O O	....	Weight 146 pounds.
17	100	168	115	2375	53 (4 doses)	— — —	tr. tr. O		
18	100	168	115	2375	53 (4 doses)	— — —	O tr. O	100 mg. (10.40 A.M.)	
19	100	168	115	2375	51 (4 doses)	10 10 10	O tr. O	....	Weight 146 pounds.
20	100	168	115	2375	37 (4 doses)	10 10 10	O O O		
21	100	168	115	2375	37 (4 doses)	— — —	O tr. O	95 mg. (9.40 A.M.)	
22	100	168	115	2375	23 (4 doses)	25 10 10	tr. M O	144 mg. (10.30 A.M.)	
23	100	168	115	2375	16 (3 doses)	25 10 —	O O O	....	Diarrhea.
24	100	168	115	2375	15 (3 doses)	— — 10	O O O		
25	100	168	115	2375	22 (3 doses)	12.5, 12.5, 12.5	tr. O O	....	Diarrhea.
26	100	168	115	2375	22 (3 doses)	12.5, 25.0, —	tr. M tr.		
27	100	168	115	2375	26 (3 doses)	— — 25	O tr. tr.		
28	100	168	115	2375	33 (3 doses)	12.5 12.5 25	tr. tr. tr.		
29	100	168	115	2375	30 (3 doses)	12.5 12.5 25	tr. O O	....	Headache, loose bowel, anorexia.
30	100	168	115	2375	24 (3 doses)	— — —	O tr. O		
31	100	168	115	2375	31 (3 doses)	10 10 25			
Aug. 1	100	168	115	2375	31 (3 doses)	12.5, 12.5, 25	O O O	....	Hypoglycemia, 8.00 P.M.
2	100	168	115	2375	29 (3 doses)	12.5 — —	O tr. O		
3	100	168	115	2375	37 (3 doses)	— — 12.5	O tr. O		
4	100	168	115	2375	34 (3 doses)	12.5 12.5 25	O O O		Hypoglycemia in evening. Weight 146 pounds.
5	100	168	115	2375	28 (3 doses)	12.5 12.5 25	O O O		
6	100	168	115	2375	28 (3 doses)	— — —	O O O		
7	100	168	115	2375	24 (3 doses)	12.5 12.5 25	O O O		
8	100	168	115	2375	22 (3 doses)	12.5 12.5 25	O O O	110 mg. (10.30 A.M.)	Weight 146 pounds.

M = moderate tr. = trace

Miss M. N., white, age, thirty years, height, 5 feet 0 inches; weight, 115 pounds; was admitted to Dr. McCrae's service on July 26, 1927, for observation and treatment. She had been admitted in January and in April in

diabetic coma. Apparent total irresponsibility with insulin and diet kept her in jeopardy from acidosis or hypoglycemia. A strong familial history of diabetes was found. The past illnesses were: "Childhood diseases" and a possible chronic cholecystitis, first suspected during her last stay in the hospital.

Comment. Infidelity with the diet, even when closely watched, made it impossible to maintain a normal blood sugar for any period of time. The study was planned to ascertain, if possible, the power of synthalin to prevent and to alleviate acidosis. Synthalin was given in addition to the usual amount of insulin (August 3). On the third morning, owing to loss of appetite, the former was omitted but continued at noon. At 11 A.M. she suffered symptoms of a severe hypoglycemia. No blood analyses were obtained. Insulin was stopped, temporarily, while the synthalin was continued until the following morning when a rapidly deepening acidosis was manifested. Synthalin was stopped and anticoma measures were adopted.

MISS M. N., AGE, THIRTY YEARS; HEIGHT, 5 FEET 0 INCHES; WEIGHT, 115 POUNDS.

Date.	Diet. P.	F.	C.	Cal.	Insulin, units.	Synthalin, mg.	Urines, sugar.	Blood sugar, CO_2; time.	Remarks.
July 30	60	70	60	1110	69 (3 doses)	— — —	O O M	334 —	Hypoglycemia 11.00 A.M.
31	60	70	60	1110	71 (3 doses)	— — —	O O O	....	Weight 115
Aug. 1	60	70	60	1110	71 (3 doses)	— — —	O O O		
2	60	70	60	1110	71 (3 doses)	— — —	M M tr.	50 mg. (3.00 P.M.)	Weight 115
3	60	70	60	1110	57 (2 doses)	25 10 25	O M M		
4	60	70	60	1110	75 (3 doses)	25 10 25	O M O		
5	60	70	60	1110	30 (2 doses)	— 10 25	O O tr.	....	Severe hypoglycemia at 11.00 A.M.
6	60	70	60	1110	45 (2 doses)	10 — —	tr. H H	480 mg. (NOON), 14.2 (CO_2)	Heavy acetonuria.
		Anticoma measures afternoon of Aug. 6.							
7	60	70	60	1110	75 (3 doses)	— — —	O O O		
8	60	70	60	1110	75 (3 doses)	— — —	O H tr.	496	Hypoglycemia 11.00 P.M.

H = heavy M = moderate tr. = trace

Mrs. S. D., Hebrew, age, fifty-three years; height, 4 feet 11 inches; weight, 111 pounds; was admitted to Dr. McCrae's service August 6, 1927. The chief complaints were: Vertigo, tinnitus, "palpitation of the heart," generalized pruritus, excessive appetite, nycturia and loss of weight (35 pounds in the past year). The family history was negative. Occasional "sore throats" comprised the past illnesses. Moderate undernutrition was the only positive finding on physical examination. The laboratory analyses revealed a negative Wassermann test, normal urea and creatinine contents in the blood with a slight elevation of the blood sugar. A blood analysis obtained in the dispensary a few days prior to admission revealed a sugar content of 0.284 per cent. On her admission a diet of 70 gm. protein, 80 gm. carbohydrate and 1815 calories was prescribed. On the second day of this program the blood sugar was a trifle above normal. Synthalin was begun and the carbohydrate increased rapidly.

Comment. Two days after the synthalin was used the pruritus was relieved, the blood sugar was reduced to a normal percentage on a much higher carbohydrate intake, while the protein and total calories were kept constant. A strongly positive reaction for sugar was obtained on the 4.00 P.M. specimen on the "synthalin-free day." Theoretically, we overcame this by increasing the evening dose of synthalin.

MRS. S. D., AGE, FIFTY-THREE YEARS; HEIGHT, 4 FEET 11 INCHES; WEIGHT, 111 POUNDS.

Date.	Diet. P.	F.	C.	Cal.	Insulin, units.	Synthalin, mg.	Urine, sugar.	Blood sugar.	Remarks.
Aug. 6	...	...	...	....	....	....	....	....	Admitted.
7	70	135	80	1815	— —	— —	O O O	128 mg.	Weight 111 pounds.
8	70	135	80	1815	—	—	O O O		
9	70	135	80	1815	—	—	O O O		
10	70	135	80	1815	—	10 10 10	O O O		
11	70	135	118	1967	—	10 10 10	O O O		
12	70	135	140	2055	— —	— — —	O O H	101 mg.	
13	70	107	158	1875	—	10 10 25	O O O		
14	70	100	178	1892	—	10 10 25	O O O	110 mg.	Weight 110 pounds.
15	70	90	198	1900	—	— — —	O O O	110 mg.	
16	70	90	198	1900	—	— — —	O O O	110 mg.	

H = heavy

MRS. T. A., AGE, THIRTY-EIGHT YEARS; HEIGHT, 5 FEET 3 INCHES; WEIGHT, 124 POUNDS.

Date.	Diet. P.	F.	C.	Cal.	Insulin, units.	Synthalin, mg.	Urine, sugar.	Blood sugar, CO_2: time.	Remarks.
June 28	70	137	70	1800	49 (3 doses)	— — —	tr. O O	160 mg. (11.00 A.M.)	Weight 124 pounds.
29	70	137	70	1800	47 (3 doses)	— — —	tr. O O		
30	70	137	70	1800	45 (3 doses)	— — —	tr. O O		
July 1	70	137	70	1800	47 (3 doses)	— — —	tr. tr. O		
2	70	137	70	1800	46 (3 doses)	— — —	tr. tr. O		
3	70	137	70	1800	48 (3 doses)	— — —	tr. O O		
4	70	137	70	1800	50 (3 doses)	— — —	tr. — O		
5	70	137	70	1800	47 (3 doses)	— — —	O O O		
6	70	137	70	1800	47 (3 doses)	— — —	— — —		
7	70	137	70	1800	48 (3 doses)	— — —	tr. O O		
8	70	137	70	1800	48 (3 doses)	— — —	tr. O O		
9	70	137	70	1800	50 (3 doses)	— — —	O O O		
10	70	137	70	1800	50 (3 doses)	— — —	O O O		
11	70	137	70	1800	47 (3 doses)	— — —	tr. O O		
12	70	137	70	1800	47 (3 doses)	— — —	tr. O O		
13	70	137	70	1800	49 (3 doses)	— — —	tr. O O		
14	70	137	70	1800	47 (3 doses)	— — —	tr. O O		
15	70	137	70	1800	47 (3 doses)	— — —	tr. O O		
16	70	137	70	1800	46 (3 doses)	— — —	tr. O O		
17	70	137	70	1800	44 (3 doses)	— — —	tr. O O		
18	70	137	70	1800	44 (3 doses)	— — —	tr. tr. O		
19	70	137	70	1800	46 (3 doses)	— — 10	tr. O O	95 mg. (10.00 A.M.)	Weight 124 pounds.
20	70	137	70	1800	41 (3 doses)	10 — 10	O O O		
21	70	137	70	1800	44 (3 doses)	10, 10, 10	O O O		
22	70	137	70	1800	43 (3 doses)	10, 10, 25,	tr. O O		
23	70	137	70	1800	37 (3 doses)	— — —	O O O		
24	70	137	70	1800	33 (3 doses)	10, 10, 10,	O O O		
25	70	137	70	1800	32 (3 doses)	10, 10, 25,	tr. O O		
26	70	137	70	1800	28 (3 doses)	10, 25, 10	O O O	....	Nauseated.
27	70	137	70	1800	32 (3 doses)	— — —	tr. O O		
28	70	137	70	1800	31 (2 doses)	25, 10, 25	tr. O H		
29	70	137	70	1800	32 (3 doses)	25, 12.5 —	O O O	....	Nauseated, diarrhea.
30	70	137	70	1800	32 (3 doses)	— — —	O O O		
31	70	137	70	1800	32 (3 doses)	10, 10, 25	O O O		
Aug. 1	70	137	70	1800	32 (3 doses)	10, 10, 25	O O O	78 mg. (9.45 A.M.)	Weight 122 pounds.
2	70	137	70	1800	32 (3 doses)	— — —	O O O		
3	70	137	70	1800	32 (3 doses)	10, 10, 25	O O O		
4	70	137	70	1800	32 (3 doses)	10, 10, 25	tr. O O		

H = heavy tr. = trace

Mrs. T. A., white, age, thirty-eight years; height, 5 feet 3 inches; weight, 124 pounds; gives a history of diabetes dating from April, 1925. Loss of weight, excessive thirst and polyuria were the only symptoms. Her mother is suffering from diabetes, otherwise the family history is negative. Scarlet fever in childhood was the only past illness. Following the diagnosis of diabetes she received institutional treatment in April, 1925. The diet was weighed and insulin taken for a short period. Further hospital treatment was necessary in December, 1925, during and after which the diet was weighed and insulin continued. In January, 1926, her first pregnancy ended (8 months). The baby lived two weeks.

Irregular meals, and time of insulin administration, detract from the experimental value in this instance. We have, however, an illustration (see Table, Mrs. T. A.) of the decrease of insulin, the loss of body weight and the increased ease with which the diabetes could be controlled. A "home record" shows that the loss of weight occurred only during the period when symptoms of synthalin overdosage were present. Synthalin was stopped September 13, 1927, and up to the present time, September 23, the insulin requirement has increased from 32 units to 41, 4 units below the presynthalin dosage.

MISS M. MC K., AGE, FIFTEEN YEARS; HEIGHT, 4 FEET 11 INCHES; WEIGHT, 102 POUNDS.

Date.	Diet. P.	F.	C.	Cal.	Insulin, units.	Synthalin, mg.			Urine, sugar.			Blood sugar, CO_2 time.	Remarks.
July 13	80	128	80	1800	24 (3 doses)	—	—	—	O	O	O		
14	80	128	80	1800	24 (3 doses)	—	—	—	O	O	O		
15	80	128	80	1800	24 (3 doses)	—	—	—	O	O	O		
16	80	128	80	1800	24 (3 doses)	—	—	—	O	tr.	M		
17	80	128	80	1800	24 (3 doses)	—	—	—	O	O	O		
18	80	128	80	1800	24 (3 doses)	—	—	—	—	—	—	75 mg. (10.00 P.M.)	Weight 102 pounds.
19	80	128	80	1800	24 (3 doses)	10	10	10	O	tr.	tr.		
20	80	128	80	1800	24 (3 doses)	10	10	25	O	O	M	....	Nauseated 8.00 P.M.
21	80	128	80	1800	24 (3 doses)	—	—	—	tr.	O	O	....	Poor appetite.
22	80	128	80	1800	24 (3 doses)	—	—	10	O	O	tr.		
23	80	128	80	1800	24 (3 doses)	10	10	10	O	O	tr.		
24	80	128	80	1800	24 (3 doses)	—	—	—	O	O	tr.		
25	80	128	80	1800	22 (3 doses)	10	12.5	12.5	O	M	H		
26	80	128	80	1800	24 (3 doses)	12.5	12.5	12.5	O	O	O	....	Appetite poor.
27	80	128	80	1800	20 (3 doses)	—	—	—	O	O	O	....	Weight 100 pounds.
28	80	128	80	1800	20 (3 doses)	10	10	10	O	O	O		
29	80	128	80	1800	20 (3 doses)	10	10	10	O	O	O		
30	80	128	80	1800	16 (3 doses)	—	—	—	O	O	O		
31	80	128	80	1800	16 (3 doses)	10	10	10	O	tr.	O		
Aug. 1	80	128	80	1800	14 (3 doses)	10	10	10	O	O	O		
2	80	128	80	1800	14 (3 doses)	—	—	—	O	O	O	82 mg. (10.30 A.M.)	
3	80	128	80	1800	10 (2 doses)	10	10	10	O	O	O		

H = heavy M = moderate tr. = trace

Miss M. McK., age, fifteen years; height, 4 feet 11 inches; weight, 102 pounds; gave a history ofdiabetes dating from March, 1925, with rapid progression of the disorder three months prior to its discovery. The family history was negative. Measles, chicken pox, mumps and whooping cough which antedated the diabetes comprised the past illnesses. The physical examination in October, 1926, was negative. Treatment was begun, under Dr. F. M. Allen, in August, 1925. A weighed diet and insulin were used, On her discharge the diabetes was under control. The diet, 80 gm. protein, 80 gm. carbohydrate and 1800 calories, with 38 units of insulin daily, was continued. The dosage was increased to 46 units during the fall of 1926.

With myrtillin added to the treatment the new level became stationary for a period of months at 24 units, given in three doses. Synthalin was begun on July 19 (see Table, M. McK.). Symptoms of overdosage appeared the following evening without rendering the urine free from sugar. A reduction of 2 units, July 25, after a day free from synthalin, resulted in heavy glycosuria. This rapidly subsided when the 2 units were resumed with a heavier dosage of synthalin. A total of 72.5 mg. of synthalin in two days permitted a reduction of 4 units of insulin. Freedom from glycosuria was maintained by 60 mg. in two days until further insulin reductions, July 16 and 17, caused a transitory glycosuria. The smaller dosage of synthalin, with no symptoms of overdosage, permitted a more rapid reduction of insulin, July 27 to August 3. During the latter part of August symptoms of synthalin overdosage were prominent. The insulin requirement increased. Relief was obtained by giving decholin and the insulin dosage dropped.

Comment. The lessened effect of synthalin on urine sugar in the presence of symptoms of overdosage, the reduction of insulin which had hitherto been impossible, the elimination of one dose daily and loss of body weight are illustrated.

Miss L. M., school teacher, white, age, twenty-eight years; height, 5 feet 5½ inches; weight, 104 pounds; referred by Dr. H. Kistler, was seen December 11, 1926. The chief complaints were: Fatigue, excessive appetite, dryness of the mouth, thirst and loss of weight. The symptoms had been considerably alleviated with a low-carbohydrate diet, prescribed by her family physician. Father died recently (apoplexy) and a maternal aunt is suffering from diabetes. Her past illnesses were: Measles, whooping cough and scarlet fever in childhood, and quinsy each winter while attending high school. The present illness dates from December, 1925, when headache was the chief symptom, though some increase of appetite, thirst and polyuria were present. Her eyes, examined at that time, were ruled out as a cause for the headaches. The only abnormalities found on physical examination were: Rather marked undernutrition, dryness of the skin and diseased tonsils. Laboratory analyses revealed a plasma sugar of 0.235 per cent, a urea of 0.014 per cent, with a strongly positive reaction for sugar and a faint reaction for acetone in the urine. On December 12, a weighed diet, 70 gm. protein, 60 gm. carbohydrate and 1800 calories, with 12 units of insulin was begun. The diet was increased to 80 gm. protein, 70 gm. carbohydrate and 2000 calories; and the insulin to 14 units, December 15. Eventually 14 units, in two doses, proved to be almost sufficient until synthalin made a reduction possible.

Comment. Blood and urine tests for sugar subsequent to the supplementing of synthalin in the treatment, July 8, were normal. The reduction and discontinuance of the insulin were not attended by a return of glycosuria.

Synthalin, in doses of 10 mg., three times daily, omitting every third day, produced no untoward results. A total dosage, however, of 60 mg. in one day was followed by loss of appetite and nausea. On the appearance of symptoms of overdosage, synthalin was discontinued for a twenty-four-hour period. In this instance distaste for fat and anorexia were the first symptoms of a toxic dosage of synthalin. Synthalin was stopped August 19, and insulin resumed. At the present time, September 23, 1927, 36 units (22 above the "pre-synthalin" dosage) are required, to maintain a normal blood-sugar level. A gain in weight and an increase in the diet to 90 gm. protein, 110 gm. carbohydrate and 2400 calories probably account for the higher dosage.

MISS L. M., AGE, TWENTY-EIGHT YEARS; HEIGHT, 5 FEET 5½ INCHES; WEIGHT, 104 POUNDS.

Date.	Diet. P.	F.	C.	Cal.	Insulin, units.	Synthalin, mg.	Urine, sugar.	Blood sugar, CO_2; time.	Remarks.
June 4	80	142	100	2000	18 (2 doses)	– – –	O O	76 mg. (10.30 A.M.)	Weight 104 pounds.
5	80	142	100	2000	18 (2 doses)	– – –	O O		
6	80	142	100	2000	18 (2 doses)	– – –	O O	....	Mild hypoglycemia in P.M.
7	80	142	100	2000	16 (2 doses)	– – –	O O		
8	80	142	100	2000	14 (2 doses)	– – –	O O		
9	80	142	100	2000	14 (2 doses)	– – –	O O		
9 to 16	80	142	100	2000	14 (2 doses)	– – –	O O		
17	80	142	100	2000	14 (2 doses)	– – –	O tr.		
18	80	142	100	2000	14 (2 doses)	– – –	O M		
19	80	142	100	2000	14 (2 doses)	– – –	O O		
20	80	142	100	2000	14 (2 doses)	– – –	tr. O		
21	80	142	100	2000	14 (2 doses)	– – –	O O		
22	80	142	100	2000	14 (2 doses)	– – –	– O		
23	80	142	100	2000	14 (2 doses)	– – –	O tr.		
24	80	142	100	2000	14 (2 doses)	– – –	tr. O		
25	80	142	100	2000	14 (2 doses)	– – –	O tr.		
26	80	142	100	2000	14 (2 doses)	– – –	O tr.		
27	80	142	100	2000	14 (2 doses)	– – –	tr. tr.	98 mg. (3.40 P.M.)	Weight 104 pounds.
28	80	142	100	2000	14 (2 doses)	– – –	tr. –		
From June 28 to July 5 record unchanged.									
July 6	80	142	100	2000	14 (2 doses)	10 10 10	tr. –		
7	80	142	100	2000	14 (2 doses)	10 10 10	O O		
8	80	142	100	2000	14 (2 doses)	– – –			
9	80	142	100	2000	14 (2 doses)	10 10 10	O O		
10	80	142	100	2000	14 (2 doses)	10 10 10	O O		
11	80	142	100	2000	14 (2 doses)	– – –	O O		
12	80	142	100	2000	14 (2 doses)	10 10 10	O O		
13	80	142	100	2000	14 (2 doses)	10 10 10	O O		
14	80	142	100	2000	14 (2 doses)	10 10 10	O O	100 mg. (10.00 A.M.)	
15	80	142	100	2000	14 (2 doses)	– – –	O O	....	Weight 103 pounds.
16	80	142	100	2000	14 (2 doses)	25 10 25	O O	....	Nauseated all evening.
17	80	142	100	2000	12 (2 doses)	– – –	O O	....	Insulin reduced.
18	80	142	100	2000	8 (2 doses)	– 10 25	O O	....	Insulin reduced.
19	80	142	100	2000	4 (1 dose)	25 – –	O O	....	Insulin reduced.
20	80	142	100	2000	4 (1 dose)	10 – 10	O O	....	Weight 101 pounds.
21	80	142	100	2000	4 (1 dose)	10 – 10	O O		
22	80	142	100	2000	O	10 – 10	O O	....	Insulin discontinued.
23	80	142	100	2000	O	– – –	O O		
24	80	142	100	2000	O	10 10 10	O O		
25	80	142	100	2000	O	10 10 10	O O		
26	80	142	100	2000	O	– – –	O O		
27	80	142	100	2000	O	10 10 10	O O	88 mg. (9.30 A.M.)	Weight 101 pounds.

M = moderate tr. = trace

The writer wishes to record the observations of this preliminary study, as impressions only. The material is not large enough or the study of sufficient duration to warrant conclusions. Further observations over a long period of time, including respiratory quotient estimations and liver function studies, will demonstrate the place synthalin is to receive as an adjunct in the treatment of diabetes. The effects of synthalin early in the treatment should be carefully differentiated from a return of tolerance independent of its use, a caution pointed out by Joslin.[10] The long standing control of several of these cases, and the prompt appearance of glycosuria on discontinuing the synthalin, eliminates the likelihood of confusion.

Summary. In this group of 7 patients the following findings were outstanding:

1. The regularity in the reduction of insulin.
2. The reduction in the number of doses of insulin in 4 of the 6 "insulin patients."
3. The elimination of insulin entirely in two instances. These patients were undernourished so not in the group where insulin reduction is usual.
4. The symptoms of synthalin overdosage were: Loss of appetite, 3; metallic taste in the mouth, 1; distaste for fat, 1; distaste for lean meat, 1; looseness of the bowels, 3; headache, 1; nausea, 3; loss of weight, 5.
5. The increased insulin requirement upon the onset of symptoms of synthalin overdosage.
6. The decreased insulin requirement upon relief from overdosage symptoms (case M. McK.).
7. The symptoms of synthalin overdosage were alleviated and a larger dosage permitted in two instances, by giving 0.5 m. sodium dehydrocholate (decholin) with each administration.
8. The loss of weight in all but one instance when symptoms from excessive doses of synthalin were prominent.
9. The large increases in the carbohydrate intake without return of hyperglycemia (case S. D.).
10. The synthalin was slower in its effect than insulin. The effect, however, was more prolonged. It cannot be used as a substitute for insulin in the treatment of coma nor will it prevent a patient, with severe diabetes, from going into coma.
11. It in no way detracts from the necessity for accurate dietetic control with proper distribution and timing of insulin administration.

Conclusions. From these preliminary observations the writer suggests that more conservative doses than were used at first in these cases, would lead to fewer disappointments. Ten milligrams of synthalin, three times daily before meals, for two successive days, omitting the third day, serves as a starting point with adults. As the doses are increased, strict instructions to stop all synthalin for twenty-four hours in event of *even the mildest* symptoms of overdosage appearing, should be given. The same dosage may be resumed after a twenty-four-hour rest if decholin is used. If it is not, a lower level should be maintained to prevent the toxic effects of synthalin.

There is no doubt but that synthalin affects the level of the blood-sugar. Whether treatment over a period of years will prove detrimental or not, has yet to be proved. At the present one feels justified in using synthalin in every case of diabetes. If there is a substantial reduction in the insulin or an elimination of one or all doses, the additional bother and expense (if any) seem warranted.

On the other hand, if proper facilities for educating the patient are not available, or if the total unitage of insulin is reduced and not the number of doses, the simpler method seems more applicable. Oral administration is the chief relief to the patient but probably the best feature of its use is that it enlarges the "noninsulin" group of diabetic patients.

BIBLIOGRAPHY.

1. Frank, E., Nothmann, M., and Wagner, A.: Ueber synthetisch dargestellte Körper mit insulinartiger Wirkung auf den normalen und diabetischen Organismus, Klin. Wchnschr., 1926, **5**, 2100.
2. Frank, E.: Verh. d. Ges. f. Verdauungs u. Stoffwechsehranheiten, 1926, **6**, 187.
3. Morawitz, P.: Münch. med. Wchnschr., 1927, **23**, 571.
4. Adler, A.: By Effects of Synthalin, Klin. Wchnschr., 1927, **6**, 493.
5. Rabinowitch, I. M.: Observations on the Use of Synthalin in the Treatment of Diabetes Mellitus, Can. Med. Assn. J., 1927, **27**, 901.
6. Lorenzen, J. N.: Ugesk. f. Laeger, 1927, **89**, 322 (abstract, J. Am. Med. Assn., 1927, **88**, 260).
7. Carrasco, R. Formiguera: Synthalin in Diabetes, Rev. med. de Barcelona, 1927, **7**, 246.
8. De Jong, J. J.: Synthalin, Ned. Tydschr. v. Geneesk., 1927, **71**, 541.
9. Priesel, R. and Wagner, R.: Synthalin in Children, Klin. Wchnschr., 1927, **6**, 884.
10. Joslin, E. P.: Paper read before Society of Clinical Investigation, Atlantic City, 1927.

SICKLE-CELL (DREPANOCYTIC) ANEMIA.

With Report of a Second Case Successfully Treated by Splenectomy and Further Observations on the Mechanism of Sickle-cell Formation.

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Since Herrick[1] discovered sickle-cell anemia in 1910, there have been published some twenty articles describing the clinical features of the disease and reporting the peculiar behavior of the red blood corpuscles of affected individuals under various laboratory conditions. My purpose in this article is not to add another description of sickle-cell anemia to those already published, but rather to report a second case benefited by splenectomy, to add a few new facts regarding the behavior of sickle cells, and to suggest a correlation of data previously reported as isolated observations.

Sickle-cell anemia occurs only in the negro race. Its incidence clearly indicates a specific hereditary predisposition. Its essential feature is the occurrence in the blood of crescentic red blood cor-

puscles or their development from apparently normal red blood corpuscles under suitable conditions outside the body. The clinical picture closely resembles that of familial hemolytic jaundice. The following differences, however, are noteworthy: In sickle-cell anemia the resistance of the red blood corpuscles is increased or normal, whereas in familial hemolytic jaundice it is markedly decreased; in sickle-cell anemia the spleen is only occasionally enlarged, whereas in familial hemolytic jaundice it is usually enlarged; in sickle-cell anemia there are usually certain features not present in familial hemolytic jaundice, such as leg ulcers, joint pains, and crises of abdominal pain.

Red blood corpuscles which become distorted into elongated and crescentic forms, commonly called "sickle cells," are not limited to individuals with anemia but are found in perfectly healthy negroes among whose relatives may usually be found a case or two of sickle-cell anemia. The condition of having red blood corpuscles which are susceptible to the sickle-cell distortion, unattended by anemia, has generally been called "latent sickle-cell anemia." This name is obviously inapplicable. It is difficult even, to conceive of a latent anemia. The qualifying adjective "incipent" would be no better, for some of these individuals live out their normal expectancies without ever developing anemia. In this article I use the term "sickle-cell trait" instead of the misleading one "latent sickle-cell anemia."

There can now be no doubt that the peculiar susceptibility of red blood corpuscles to form sickle cells is hereditary and is carried throughout life. Apparently, the susceptibility is transmitted as a dominant unit character according to the Mendelian law. Its incidence among negro dispensary patients, regardless of their ailment, has been reported as about 7 per cent.[2] The ethnologic origin of the sickle-cell trait is entirely unknown.

Relation between the Sickle-cell Trait and Sickle-cell Anemia. Most writers tacitly assume that the occurrence of sickle cells in the blood is related to the establishment of severe anemia. The fact that severe hemolytic anemia occurs much more frequently among negroes with the sickle-cell trait than among negroes without it, goes far to prove this assumption. The anemia is associated with a group of clinical features which is seemingly specific for individuals with the sickle cell trait. Finally, sickle cells are seldom found in dried blood smears, or in wet smears examined immediately from nonanemic subjects with the sickle-cell trait, whereas, they are found in such blood smears from patients with sickle-cell anemia.

It has been stated that there is no proportionality between the number of sickle cells and the severity of symptoms. This statement is misleading unless it is understood that it has reference to the number of sickle cells observed in wet smears after standing hours or days. In other words, there is no difference in the ability of the

red corpuscles of anemic and nonanemic subjects with the sickle-cell trait to form sickle cells outside the body under suitable conditions, but there is an important difference between the two classes of subjects in that in the nonanemic, sickle cells in considerable numbers do not occur preformed in the circulating blood, whereas, in the anemic they do.

The manner in which the formation of sickle cells in the body leads to the development of severe anemia is a problem for investigation. The most obvious working hypothesis is that the red corpuscles are so injured in becoming sickle cells that thereafter they are abnormally susceptible to the ordinary hemolytic processes of the body. Several reported observations support this idea.

Sydenstricker[3] observed vigorous phagocytosis of sickle cells by large mononuclear leukocytes *in vitro*. Emmel's[4] observation of excessive phagocytosis of red corpuscles in the stained blood smears of patients with sickle-cell anemia is of less value in this connection as it is not clear whether the red corpuscles were sickle cells or had ever been sickle cells.

Cooley and Lee[2] reported that the sickle cells of wet smear cultures are rapidly destroyed at incubator temperature, whereas the normal appearing red corpuscles of the same blood smear are not. They further reported that blood of patients with sickle-cell anemia manifests hemolysis more rapidly at incubator temperature than does normal blood. When the susceptible corpuscles are suspended in normal serum or in serum from a patient with acquired hemolytic jaundice, the accelerated hemolysis is still apparent. However, if normal red corpuscles are suspended in serum from a patient with sickle-cell anemia, hemolysis is not accelerated. Cooley and Lee, therefore, drew the inference that the accelerated hemolysis is not due to increased hemolytic agents in the serum but is due to increased susceptibility of the corpuscles to hemolytic influences. Before it can safely be concluded that the sickle-cell distortion is the primary factor in the excessive blood destruction observed clinically, it remains to be demonstrated that the corpuscles become sickle cells prior to hemolysis.

Mechanism of Sickle-cell Formation in Vitro. If the distortion of red corpuscles into sickle cells be the primary factor in the blood destruction of sickle-cell anemia, it becomes important to discover what factors cause the distortion. Hahn and Gillespie[5] rendered a detailed report of a laboratory investigation of this problem. In brief the facts are as follows.

When red corpuscles of an affected individual are suspended in a hanging drop of normal saline solution in an atmosphere without oxygen, the corpuscles all assume the crescentic shape. When oxygen is admitted to the chamber[6] under the hanging drop, the corpuscles, now sickle cells, immediately revert to a circular form. The corpuscles may be put through as many transformations as one

wishes by turning into the chamber alternate streams of carbon dioxid and oxygen. Not only carbon dioxid but ethylene, nitrous oxid, nitrogen, and hydrogen are suitable to induce the distortion of the corpuscles. However, certain conditions of hydrogen-ion concentration must be met before the distortion will occur. In alkaline suspensions, the distortion occurs slowly or not at all. Acidity favors the distortion.

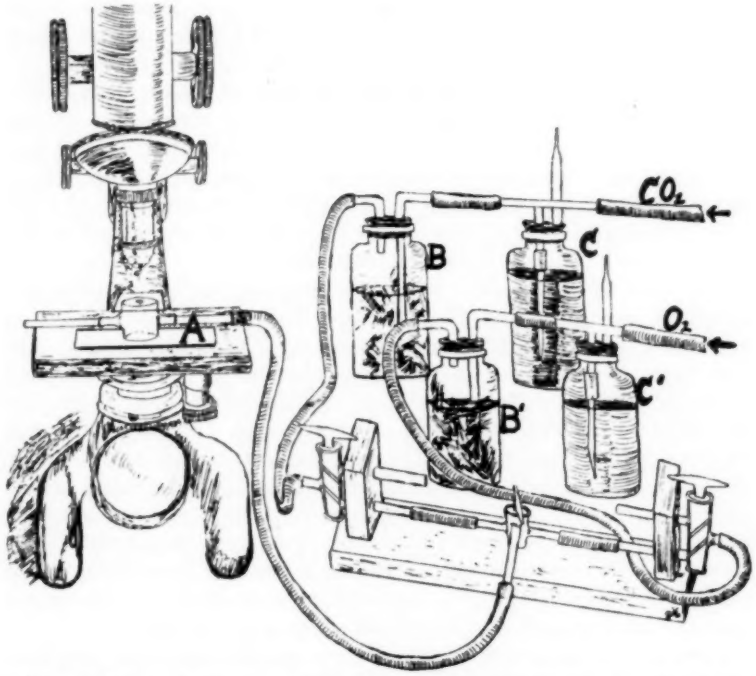

FIG. 1.—Sketch of the apparatus used to demonstrate the transformation of susceptible red corpuscles into sickle cells and to test their reactions to various gases. *A*, "Micro slide for molds, Will Corporation, No. 11812." *B* and *B'*, wash bottles for moistening the gases. *C* and *C'*, bottles arranged to act as outlets for excessive pressure and provided with water seals.

Carbon monoxid acts as effectively as oxygen in restoring sickle cells to a circular form, and after carbon monoxid has acted, carbon dioxid again induces the sickle-cell distortion. Apparently, the crescentic shape is stable when the contained hemoglobin is in the reduced state and the circular shape is stable when the hemoglobin is combined. The effect of hydrogen-ion concentration upon the distortion is thus explained, for it is known that the dissociation of combined hemoglobin is favored by increase of acidity.

It seems probable that the formation of sickle cells from susceptible corpuscles under a sealed cover slip is due to progressive decrease

of oxygen and accumulation of carbon dioxid resulting from the metabolism of the blood cells. The observation of Hein, McCalla, and Thorne[7] that the elevation of a cover slip under which sickle cells have formed causes them to revert to a circular form is consistent with this hypothesis. It has been suggested that the mechanical effect of the cover slip pressing upon the blood film is a factor in producing the distortion. Inasmuch as a mechanical factor might be suspected in a hanging drop, which in practice was really a rather thin film, it appeared important to demonstrate the sickle-cell distortion in a suspension of considerable bulk in which the corpuscles could not possibly be affected by solid surfaces.

Sickle-cell Distortion in Bulk and Fixation of Sickle Cells. The demonstration of sickle cells in a suspension of corpuscles, treated by bubbling carbon dioxid through it, is complicated by the fact that specimens withdrawn for microscopic examination are necessarily subjected to the action of atmospheric oxygen. To obviate this difficulty, a search was made for fixing agents which would preserve sickle cells in their characteristic form.

Mr. J. Greist and Mr. J. Hord, working in this laboratory, arranged an apparatus for bubbling carbon dioxid through a suspension of susceptible corpuscles in an Erlenmeyer flask. The flask was equipped with a separatory funnel for the introduction of liquid fixing agents and with an additional glass tube for the introduction of carbon dioxid charged with formaldehyde gas. Suspensions were treated with pure carbon dioxid until change of color indicated reduction of the hemoglobin. The fixing agents were than applied. In all the experiments, the liquid fixing agents were deprived of dissolved oxygen by prolonged treatment with a stream of pure carbon dioxid. After an interval of time for thorough fixation of the corpuscles, the suspensions were aërated. Specimens were then withdrawn and examined under a cover slip.

Ferrous ammonium sulphate solution and formaldehyde gas both effectively fixed sickle cells in their characteristic form. After these agents had acted, oxygen no longer restored the circular form. This result established both the facts that sickle cells are susceptible of fixation and that susceptible corpuscles can be transformed into sickle cells by exposure to carbon dioxid while they are freely suspended in normal saline solution without the intervention of any mechanical factors.

Zenker's solution and mercuric chlorid invariably fixed the corpuscles in a circular form. It will be noted that both these substances are capable of acting as oxidizing agents.

Sickle-cell Formation Independent of Serum. Josephs[8] reported that susceptible red corpuscles would not form sickle cells under a cover slip if they were previously thoroughly washed free of plasma. He interpreted his experiments to establish the fact that there is a substance in all serum essential to the sickle-cell distortion.

Dr. Francis Smith repeated in this laboratory the experiments described by Josephs in part but with this change in detail, that the ability of the washed corpuscles to form sickle cells was tested in a hanging drop suspended over a gas chamber. The red corpuscles from a patient with proved sickle-cell anemia were treated by ten successive washings with normal saline solution. After each washing, the passage of carbon dioxid through the gas chamber induced the formation of typical sickle cells. These experiments fail completely to sustain the conclusion of Josephs. We find no evidence of any plasma component which affects the transformation of discoid corpuscles into sickle cells.

In criticism of Josephs' experiments, it should be noted that the formation of sickle cells under a cover slip is notoriously capricious even when drops of unaltered blood are employed. Some slides show sickle cells and other slides made at the same time and in the same way do not. The technique described by Hahn and Gillespie[5] provides a more reliable test of the ability of red corpuscles to form sickle cells.

The Pathogenesis of Sickle-cell Anemia. Sydenstricker[3] concluded that the sickle-cell trait is only a predisposing cause of sickle-cell anemia and that when anemia is present in subjects with the sickle-cell trait it is due to "factors innocuous to the normal individual." Some such theory seems to be necessary to account for the sporadic incidence of sickle-cell anemia among large groups of perfectly healthy individuals with the sickle-cell trait. The observation of Cooley and Lee[2] that there is no proportionality between the severity of sickle-cell anemia and the ability of the red corpuscles to form sickle cells (*in vitro*) also points toward the participation of some other factor or factors than the sickle-cell trait.

The discovery of the unknown precipitating factors is the chief problem of sickle-cell anemia. This discovery might point the way to a rational mode of therapy or prophylaxis. Hahn and Gillespie[5] proposed the theory that the unknown factor is anoxemia, inasmuch as they established that asphyxia of susceptible corpuscles *in vitro* causes the sickle-cell distortion. In support of this theory they cited the frequent incidence of pulmonary disease in cases of sickle-cell anemia. Recently, cases of severe sickle-cell anemia without associated pulmonary disease have been reported. My present view, therefore, is to regard a theoretical correlation between anoxemia and anemia in subjects with the sickle-cell trait as merely suggestive and worthy of the attention of those who have large numbers of cases of sickle-cell anemia available for study.

Splenectomy in Sickle-cell Anemia. The first case of sickle-cell anemia to be treated by splenectomy was reported by Hahn and Gillespie[5] in 1927. The results of the operation were spectacular. The child became symptomatically well and has remained so up to the present time except for evidences of rickets. The blood bili-

rubin and excreted urobilin decreased rapidly. The red-cell counts and hemoglobin determinations showed less rapid though marked improvement. Notwithstanding these favorable changes, the sickle-cell trait persisted without change.

My second case of sickle-cell anemia, the details of which are reported in this article, reacted to splenectomy in an even more spectacular manner from a clinical standpoint. From a cachectic infant with a profound anemia, the patient was changed within eight weeks into a well-nourished, healthy appearing subject. The only treatment was splenectomy and careful feeding. The same care with the feeding had been taken prior to operation without any result whatever. The blood bilirubin decreased to a level within the limits of normal but the red-cell count and hemoglobin showed only moderate improvement. The sickle-cell trait persisted.

A restudy of this subject was made five months after operation. The patient continued to appear perfectly healthy except for evidences of rickets. The red-cell counts and hemoglobin were still approximately at the level established during the postoperative period of eight weeks. However, the blood bilirubin showed some increase but not to the preoperative level. The sickle-cell trait persisted without change, as estimated by the gas-chamber test, and the stained smears of the blood showed numerous sickle cells.

Splenectomy in sickle-cell anemia was first suggested by Sydenstricker and Huck.[9] Sydenstricker[3] later reported that in one case splenectomy had been attempted but that the operation was not completed. In reporting a case in a boy, three and a half years of age, Dreyfoos[10] stated that he advised splenectomy, although he had no knowledge that splenectomy had ever been performed for this condition. Operation was refused. Alden[11] reported that splenectomy was advised in one case but that the operation was refused by the patient, and that in another case (the same one described by Dreyfoos) splenectomy was considered inadvisable because of the anemia. Stewart[12] reported a case treated by splenectomy but submitted no postoperative data to indicate whether the effect of the operation was good or bad.

In the light of my experience, profound anemia is no contraindication to splenectomy in sickle-cell anemia. On the contrary, it is the one most certain indication. A preliminary blood transfusion would be advisable in cases for which donors can be found. Splenectomy is not proposed as a cure for the sickle-cell trait, which in my two cases and in that of Stewart, was unaffected by the procedure. Apparently, removal of the spleen merely makes the sickle-cell trait less menacing to the life of the patient by curtailing excessive red-cell destruction.

All the indications for splenectomy are fulfilled by cases of sickle-cell anemia. Excessive hemolysis is present; compensatory activity of the hemopoietic tissues is evidenced by an excessive output of

FIG. 2.—Photomicrograph of sickle cells produced from normally appearing but susceptible red corpuscles by passing carbon dioxid through the gas chamber. The gas was passed until the hanging drop was dry. The sickle cells were then fixed by formaldehyde vapor and stained with Wright's stain.

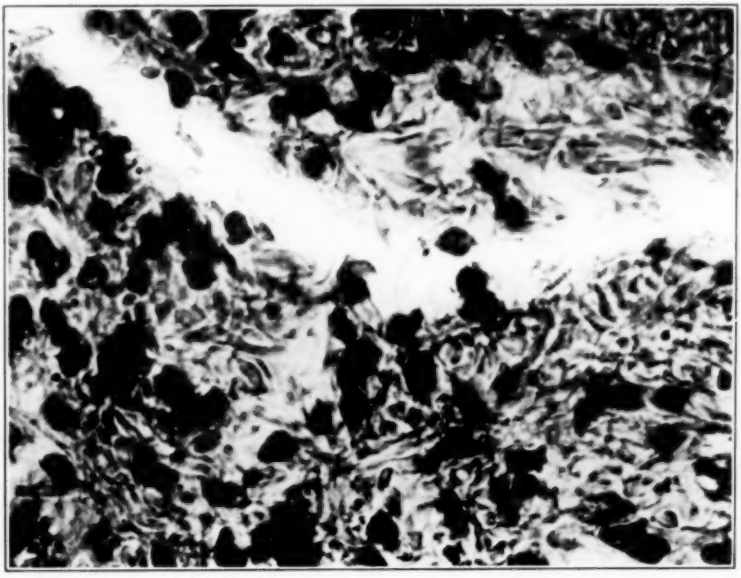

FIG. 3.—Oil immersion photomicrograph of a section of the spleen fixed in 10 per cent liquor formaldehydi. Practically all the red corpuscles are elongated and sickle-shaped. What appear to be red corpuscles of circular contour are of very small diameter and are interpreted as being transverse sections of sickle cells.

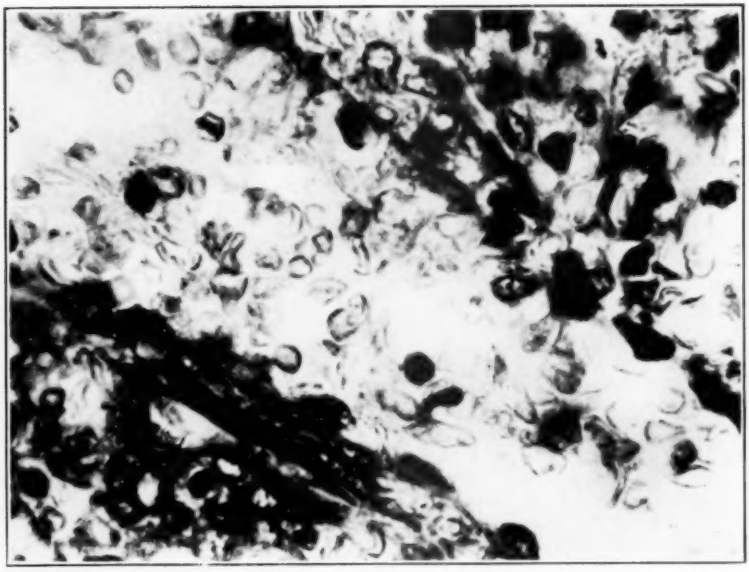

FIG. 4.—Oil immersion photomicrograph of a section of the spleen fixed in Zenker's fluid. Although many of the red corpuscles are of rather irregular outline, none have the sharp horns of sickle cells and their predominating contour is circular. These are interpreted as corpuscles reversed to a circular shape after having been sickle cells.

nucleated and reticulated red corpuscles (reticulocytes) and by high leukocyte counts; and splenic involvement is evidenced by crises of abdominal pain or by splenomegaly or by both.

The beneficial effect of splenectomy requires further explanation than can be given at the present time. It may be, as I have assumed that the removal of the spleen prevents the destruction of corpuscles which have undergone the sickle-cell distortion due to the action of an unknown extrasplenic factor. On the other hand, it is possible that splenectomy rids the body of a factor which facilitates the transformation of susceptible corpuscles into sickle cells. The fact that the corpuscles show an unaltered ability to form sickle cells *in vitro* after splenectomy does not necessarily imply that sickle cells are formed in the body in such numbers after splenectomy as before. A sharp distinction must be drawn between the formation of sickle cells *in vitro* and *in vivo*.

Splenomegaly in Sickle-cell Anemia. In some articles on sickle-cell anemia the impression is left that splenomegaly is a regular feature of the disease. On the other hand, Huck[9] stated that the absence of splenomegaly in sickle-cell anemia serves to differentiate it from familial hemolytic jaundice. Later, Sydenstricker[3] stated that of 71 cases, 11 had splenomegaly. I find that approximately 15 per cent of the reported cases had splenomegaly. It is, thereforel obvious that the size of the spleen is of no service in the differentia, diagnosis. In the case reported by Dreyfoos,[10] the spleen was at one time not palpable but later became so. In the case reported by Stewart,[12] the spleen was at first not palpable, later became so, and still later decreased in size until it was again not palpable. In this case, the liver also decreased in size relative to the size of the body of the growing child. It is likely that the size of the spleen is variable depending upon the stage of the disease. Such pathologic descriptions as are available indicate that the splenic lesion is one of intense congestion with red cells and of tissue damage revealed eventually by fibrosis, pigmentation, and healed infarcts. No observer has reported any significant cellular hyperplasia. The entire picture is one of an overworked, badly damaged spleen.

Whether the size of the spleen has any bearing upon the advisability of splenectomy remains to be seen. The spleen was large in both of my cases and the results of splenectomy were excellent. It may be that cases with small, atrophic spleens will not respond so well.* The matter must be put to clinical test. A present, it would be irrational to withhold splenectomy in a case of sickle-cell anemia in which the spleen is not palpable. We do not know how closely the size of the spleen is correlated with its hemolytic activity, although presumably a small fibrotic spleen is not apt to be functioning excessively.

* In Stewart's[12] case, seen by one of us at operation, the child's spleen was extremely small and fibrotic and very slight improvement followed its removal.—EDS.

R. W. R., colored, aged eighteen months, was admitted to the Indianapolis City Hospital July 3, 1926, with a complaint of persistent cough, drowsiness, and vomiting. His illness dated from April, 1926, when these symptoms led to a diagnosis of bronchopneumonia. Since that date, the patient had steadily lost weight. He was brought to the hospital and kept under observation from May 8 to June 10. In the record of the "previous admission" are mentioned the following observations: Severe anemia, evidence of rickets, marked cervical adenitis, râles in the upper part of the left lung, enlargement of the liver, and great enlargement of the spleen. After some clinical improvement, the patient was referred to the outpatient department for continued observation. High fever and exacerbation of the aforementioned symptoms led to readmission on July 3. On this occasion, I was invited to study the case by Dr. Winters, of the pediatric staff, who made a tentative diagnosis of sickle-cell anemia.

The patient was an emaciated colored child apparently a little more than one year of age. The skin lacked elasticity. The costal borders flared and the abdomen was large. The legs were bowed. The costochondral junctions were marked by beads. The scleræ had a peculiar greenish color. The pupils were normal in appearance and in reactions. The epitrochlear, cervical, and inguinal lymph glands were enlarged. Both lung areas had impaired resonance but no râles were heard. The heart was rapid but without adventitious sounds. The abdomen was distended but the wall was flaccid. Liver dullness extended 3 cm. below the costal border. The left hypochondrium was occupied by a firm, smooth mass in the medial border of which a notch could be felt. This mass extended to the iliac crest and to the midline. The patient's weight was 18 pounds.

TABLE I.

Date.	Red-cell count, in millions.	Hemoglobin, per cent.	White-cell count, in thousands.	Body weight in pounds.
May 14, 1926	....	..	43.3	16
May 15, 1926	....	..	40.0	
May 18, 1926	1.83			
May 28, 1926	2.38	40	9.8	18
June 4, 1926	3.04	40	10.9	
July 3, 1926	2.61	55	6.5	18
July 7, 1926	3.18	45	8.4	15
July 15, 1926	3.53	42	13.3	
Aug. 14, 1926	2.47	45	6.6	
Sept. 13, 1926		Splenectomy.		15
Sept. 21, 1926	2.55	38	35.4	
Oct. 13, 1926	3.97	..	18.9	22
Feb. 17, 1927	3.75	60	25.8	
Feb. 22, 1927	3.03	..	37.8	25

Repeated Roentgen ray examinations revealed increased density in the left lung field. The urine was negative for albumin, sugar, casts, and pus cells. Stool examination showed no ova or parasites. A blood smear (Wright's stain) showed numerous poikilocytes and nucleated red cells. Many of the poikilocytes were crescentic. Of the red cells, 6 per cent were reticulated. The differential formula was fairly uniform in eight examinations, five before and three after operation. The average values were as fol-

lows: Polymorphs, 49 per cent; lymphocytes, 46 per cent; large mononuclears, 2 per cent; eosinophils, 2 per cent; basophils, 1 per cent. The blood-cell counts are set forth in Table I. After standing one hour at room temperature, a sealed wet smear of the blood showed transformation of all the red cells into sickle cells. The results of five van den Bergh tests are set forth in Table II. The red cell resistance, as determined by hypotonic saline solutions, was increased. The values are set forth in Table III.

TABLE II.—SERUM BILIRUBIN DETERMINED BY THE VAN DEN BERG TEST.

Date.	Direct.		Indirect.	Quantitative.	
	1 minute.	1 hour.		Mg. per liter.	Units.
Sept. 2, 1926	Neg.	Pink	Pink	17.5	3.5
Sept. 13, 1926		Splenectomy.			
Sept. 18, 1926	Neg.	Pink	Pink	6.4	1.3
Oct. 13, 1926	Neg.	Neg.	Faint pink	2.0	0.4
Feb. 17, 1927	Neg.	Faint pink	Pink	10.0	2.0
Feb. 22, 1927	Neg.	Faint pink	Pink	9.75	1.97

TABLE III.—RED CELL RESISTANCE DETERMINED BY HYPOTONIC SALINE SOLUTIONS.

	Beginning hemolysis, per cent.	Complete hemolysis, per cent.
Patient's cells	0.42	0.03
Normal control	0.44	0.36

Blood transfusion could not be carried out for lack of a compatible donor. On September 13, 1926, I removed the spleen[13] through a left rectus incision. The operation was not attended by any unusual difficulties. There were few adhesions. Wound healing was satisfactory. The postoperative course was uneventful. After the first ten days, the temperature became practically normal. The child retained his feedings and began to show weight gains. His cough subsided and he became alert. On discharge he was symptomatically well.

On February 16, 1927, the patient was admitted to the James Whitcomb Riley Hospital for observation. He was symptomatically well and appeared to be well nourished. The lymphadenopathy and anatomical evidences of rickets were still present. The scleræ were very slightly greenish. The right side of the abdomen was larger than the left and the lower border of liver dullness was 3 cm. below the costal border. Roentgen ray of the lungs showed clearing of the left side but there was a slight hazy thickening of the lung markings throughout the right lung field. The heart shadow was moderately increased. Laboratory data obtained during this admission are shown in the tables. Dried blood smears (Wright's stain) showed moderate poikilocytosis. Of the red blood corpuscles, 2 per cent were sickle cells. A smear made from a drop of blood drawn from a finger when the arm was rendered cyanotic by a tourniquet showed the same percentage of sickle cells. After standing an hour at room temperature, a wet smear of blood, sealed with petrolatum, showed transformation of all the red cells into sickle cells.

EXAMINATION OF SPLEEN. The spleen, in the fresh condition, was about four times its normal size. The capsule was thickened in places and was marked by several depressed scars. The cut surface was almost gelatinous and of a very dark red color. Malpighian bodies were scarcely visible. Thin blocks of the spleen were dropped immediately into 10 per cent liquor formaldehydi and into Zenker's solution. A culture of a specimen selected under aseptic precautions showed no growth.

Microscopic study of the sections shows a marked congestion of the pulp with red corpuscles. In some areas, the pulp cells are pushed far apart by great pools of red corpuscles which are not distinct from each other but seem to be agglutinated. In these areas, there are large numbers of phagocytic cells loaded with coarse granules of blood pigment. The sinusoids contain a moderate amount of blood and do not show the congestion which is such a marked feature of the pulp. There is no increase of connective tissue. The lymphoid follicles are small in size. The red corpuscles of the tissue fixed in formaldehyd are all sickle cells. Where red corpuscles are seen with circular outline, their diameter suggests that they were sectioned transversely. In the Zenker tissue the red corpuscles are almost all of circular outline. The few elongated corpuscles which can be found have rounded poles and do not look like typical sickle cells. Many of the corpuscles in this tissue are ragged and of irregular outline. In my opinion these corpuscles were sickle cells prior to exposure to Zenker's solution. It will be recalled that sickle cells, produced *in vitro* from normally appearing red corpuscles, are not fixed in their characteristic form by Zenker's solution but are fixed in a circular form.

Conclusions. 1. Sickle-cell anemia, a disease which bears some resemblance to hemolytic jaundice, is of sporadic occurrence among negroes with the "sickle-cell trait," that is, whose red blood corpuscles become distorted into sickle-shaped cells under certain conditions.

2. The sickle-cell trait in itself is compatible with perfect health and long life. It is an hereditary characteristic, behaving as a dominant according to the Mendelian law of heredity. The term "latent sickle-cell anemia" is not logically applicable to individuals whose only abnormality is the possession of this trait.

3. The red corpuscles of negroes with the sickle-cell trait who are without symptoms form sickle cells as readily under proper conditions as do the red corpuscles of individuals with sickle-cell anemia. That is, there is no proportionality between the degree of anemia and the ability of the red corpuscles to form sickle cells *in vitro*.

4. There seems to be a correlation between the severity of sickle-cell anemia and the number of sickle cells in the circulating blood. Symptomless individuals with the sickle-cell trait have few or no sickle cells in the circulating blood.

5. It is likely that the formation of sickle cells in the blood from apparently normal red corpuscles leads to the increased hemolysis which produces sickle-cell anemia.

6. Evidence is cited to show that red corpuscles which have undergone the sickle-cell transformation are more susceptible to hemolytic influences than before their distortion.

7. Evidence is presented to show that the sickle-cell transformation *in vitro* is induced in apparently normal but susceptible red corpuscles by dissociation of their oxyhemoglobin.

8. A method is described for the production of sickle cells *in vitro* from apparently normal but susceptible red corpuscles freely suspended in normal saline solution, and for their fixation in their characteristic shape.

9. Evidence is presented that no serum component, separable from susceptible red corpuscles by washing, is necessary in the sickle-cell distortion.

10. The factors which precipitate the sickle-cell distortion in the living subject and which cause excessive hemolysis are unknown. Anoxemia is suggested as a possible factor.

11. Early splenectomy in sickle-cell anemia is advocated on the basis of two cases in which the procedure was followed by marked clinical improvement.

12. After splenectomy the sickle-cell trait persists unchanged. Red-cell destruction and the consequent anemia, however, are lessened.

13. The size of the spleen in sickle-cell anemia is variable and probably depends on the stage of the disease.

REFERENCES.

1. Herrick, J. B.: Peculiar Elongated and Sickle-shaped Red Blood Corpuscles in a Case of Severe Anemia, Arch. Int. Med., 1910, **6**, 517.

2. Cooley, T. B., and Lee, Pearl: The Sickle-cell Phenomenon, Am. J. Dis. Child. 1926, **32**, 334.

3. Sydenstricker, V. P.: Further Observations on Sickle-cell Anemia, J. Am. Med. Assn., 1924, **83**, 12.

4. Emmel, V. E.: A Study of Erythrocytes in a Case of Severe Anemia with Elongated and Sickle-shaped Red Blood Corpuscles, Arch. Int. Med., 1917, **20**, 586.

5. Hahn, E. V., and Gillespie, E. B.: Sickle-cell Anemia, Arch. Int. Med., 1927, **39**, 233.

6. The gas chamber employed in these experiments and the one recommended for testing corpuscles for the sickle-cell trait is described in the catalog of the Will Corporation as "Micro slide for molds, No. 11812."

7. Hein, Gordon E., McCalla, R. L., and Thorne, G. W.: Sickle-cell Anemia, Am. J. Med. Sci., 1927, **173**, 763.

8. Josephs, H. W.: Sickle-cell Anemia, Bull Johns Hop. Hosp., 1927, **40**, 77.

9. Sydenstricker, V. P.: Sickle-cell Anemia, South. Med. J., 1924, **17**, 177. The opinion of J. G. Huck was given in his discussion of this paper.

10. Dreyfoos, Max: Sickle-cell Anemia, Arch. Pediat., 1926, **43**, 436.

11. Alden, H. S.: Sickle-cell Anemia; Report of Two Cases from Ohio Illustrating its Hemolytic Nature, Am. J. Med. Sci., 1927, **173**, 168.

12. Stewart, W. B.: Sickle-cell Anemia; Report of a Case with Splenectomy, Am. J. Dis. Child., 1927, **34**, 72.

13. The patient was routinely assigned to the surgical service of Dr. T. B. Noble, Jr., through whose courtesy I had the privilege of operating.

HEREDITY IN HEMOPHILIA.

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Although there are numerous pedigrees showing the inheritance of hemophilia, there still seems to be considerable uncertainty on two points in this connection; (1) whether the female can exhibit true hemophilia, and (2) whether the male can transmit the disease. As to the former, there are numerous cases of hemophilia occurring in the female, which have been reported in the literature, but since practically all cases of bleeding were formerly listed as hemophilia, no differential diagnosis being made between that and hemorrhagic purpura, or telangiectasia, it is quite probable that few or none of the so-called cases of hemophilia in the female were true hemophilia. For an absolute diagnosis of hemophilia today, there must be the necessary laboratory findings with respect to the platelet count, coagulation time, bleeding time, and so forth. Theoretically, however, hemophilia in the female is as possible as is color blindness, for instance.

As to the possibility of the male transmitting the disease, there is also some doubt. It is recognized by all that the male does not transmit the disease as an evident one to any of his children, but the question has been whether he could transmit it to a grandson through his daughter. That some defects, such as color blindness, usually found only in the male, can be so transmitted is well known, but hemophilia has been regarded by most as an exception to this rule. Hence the formulation of Lossen a half century ago that all the descendants of hemophilic males will be absolutely free from the defect of their progenitor. In 1911, Bulloch and Fildes, reviewing the subject very thoroughly, arrived at the conclusion that there is no adequate proof that inheritance of hemophilia has ever gone through the male line, even through the intermediate step of being carried latent by the daughter of the affected male. In other words, if a male, who is a true hemophilic, survive long enough to marry and reproduce he may do so with a certain knowledge that he will never have descendants who exhibit his defect.

It is to refute such a statement, and to set forth the manner of inheritance of hemophilia that the present note is written. To geneticists the matter is clear; to clinicians who are not primarily trained in this science, and who have as their guide only the deductions which can be drawn from collected pedigrees, there does seem to be some justification for Lossen's rule. It is true that in recent years, since the diagnosis of hemophilia is dependent upon

definite laboratory findings, and not merely upon an undue tendency to bleed, there have been very few cases of transmission through the male line; it is practically always through the female that the thread of inheritance runs. In the far-famed Mampel family which has been recently brought up to date through the sixth generation by Klug, there is no real transmission through the male line, and in an article reported by Davidson and McQuarrie, in which the history extended through eight generations, there was no evidence that the male transmitted his affliction to his descendants.

It is necessary, however, to understand the transmission of sex-linked recessive characters, of which hemophilia is one, to grasp the full significance of this apparent inability of the male to pass on this very tragic defect. First of all, it is obvious that the afflicted male must live long enough to marry, and he must also have children before his ability to transmit his defect can be determined.

Mating.	Parents.		Offspring.	
	Female.	Male.	Female.	Male.
1	XX (normal)	X (normal)	XX (normal)	X (normal).
2	XX (normal)	x (hemophilic)	Xx (normal, but carrier)	X (normal).
3	Xx (normal, but carrier)	X (normal)	XX (normal)	X (normal).
			Xx (normal, but carrier)	x (hemophilic).
4	Xx (normal, but carrier)	x (hemophilic)	Xx (normal, but carrier)	X (normal).
			xx (hemophilic)	x (hemophilic).
5	xx (hemophilic)	X (normal)	Xx (normal, but carrier)	x (hemophilic).
6	xx (hemophilic)	x (hemophilic)	xx (hemophilic)	x (hemophilic).

This table shows the six possible matings of normal and hemophilic persons. The last two are theoretical, inasmuch as true hemophilia has not yet been proven to exist in the female. X and x are sex chromosomes, the former normal, the latter carrying also the factor for hemophilia. A normal X is dominant to the hemophilic x, whose presence is thus concealed when combined with a normal X. The female possesses two sex chromosomes, one inherited from either parent, while the male possesses but one derived from his mother.

If we now refer to the table above, it is evident that even this is insufficient. If he have only sons he does not transmit his defect; he must have daughters in his family as well. (Mating 2.) But since he passes it on to his daughters as a latent and not obvious defect, the fact that the transmission has occurred is incapable of proof unless these daughters marry and have sons to whom they may transmit their latent defect as an obvious disease. (Mating 3.) Again since they can transmit freedom from the disease as readily as the disease itself, the sons have an even chance of escaping the inheritance of hemophilia. (Mating 3.) Thus, lack of hemophilia

in one or two of her sons does not establish the rule that the daughter of a hemophilic man will not have hemophilic sons. The first son may exhibit it; on the other hand she may have four or five sons all normal, each one having chanced to receive the normal instead of the defective chromosome. The greater the number of sons, the more are the chances increased that one of them at least will inherit the disease.

Summing up the conditions necessary to be fulfilled before transmission through the male line can be put to the test, they are as follows: the male must live long enough to marry, he must have daughters, who in turn must marry and produce a number of sons. If these conditions are repeatedly fulfilled and none of these grandsons inherit their maternal grandfather's defect, then it may be stated that the male probably does not pass on hemophilia to his descendants. As will be seen, however, these conditions are seldom met with.

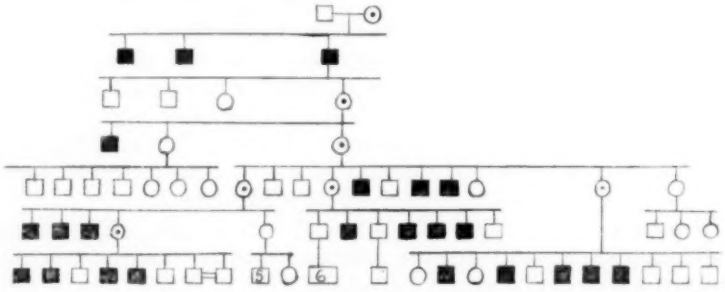
In the famous Mampel family in which the disease has run through six generations, Klug found 27 true bleeders, all males. Of these 20 died of hemorrhage before they reached the marriageable age; and 5 who lived to maturity never married. The remaining 2 married, and had daughters, but these have as yet produced no sons, hence it is impossible to put the law of Lossen to the test in this family since no opportunity has as yet arisen for the male to show whether he is capable of passing on this defect. Geneticists will watch with interest, however, the families of these daughters.

In the family history reported by Davidson and McQuarrie extending through eight generations there were 14 male bleeders. Of these 11 never married. Of the 3 who did marry, 1 had 4 sons and no daughters, hence he may be ruled out. (Mating 2.) One had a daughter who had 1 son; the other had 2 daughters, 1 unmarried and the other married, with 2 sons. Here there were three opportunities for the testing of the rule of transmission through the male, but the number of cases is entirely too small for any generalizations. The evidence being purely of a negative character, and very limited in extent, it must be held in reserve until more adequate proof is brought.

That families have been reported in which the transmission does occur through the male line at times, is well known and Bulloch and Fildes have collected these in their monograph on hemophilia. They reject them, however, as cases of true hemophilia, because the male did transmit the disease and because they were all reported before the laboratory diagnosis of hemophilia was established. That they were not justified in this procedure seems clear to me, for the study of pedigrees of other forms of hereditary bleeding, proven not to be hemophilia, do not show the clear-cut sex-linked transmission which these pedigrees show. Although hemophilia has been confused with other chronic hemorrhagic diatheses,

such as telangiectasia and hemorrhagic purpura, in these there is seldom if ever the definite sex-linked transmission through generation after generation that characterizes hemophilia. That type of inheritance through four or five generations is, next to the laboratory findings, the best guarantee of the accuracy of the diagnosis.

In a splendid article on hemophilia written by Legg in 1881, he gives a pedigree of a family through seven generations, in which the male in the second generation transmitted his defect through varying generations of females to twenty of his male descendants. (see illus.) Other pedigrees might have been chosen in which a greater number of instances of transmission through the male were exemplified, but Legg's clear differentiation of hemophilia in this family from other chronic hemorrhagic diatheses on the basis of the clinical findings leaves in my mind no doubt that he was actually dealing with hemophilia.



Pedigree, showing sex-linked mode of inheritance in hemophilia. Squares indicate males; circles, females; black symbols, persons afflicted with hemophilia; circles with dots inside, females who are normal, but carry the factor for hemophilia latent; clear symbols with numeral inside indicate a corresponding number of unaffected offspring; = means twins. Most of the hemophilic males died of hemorrhage at an early age. Note that transmission through the male in the second generation occurred, twenty of his male descendants inheriting his disease. The male inherits hemophilia from his mother, however; never from his father.

In this pedigree we see that the female in the first generation was a carrier, and the source of defect was unknown. One of her 3 sons passed on the defect to 20 descendants. One of these had 1 female intervening between him and the male progenitor who passed on the defect, 3 had 2 intervening females, 12 had 3, and 4 of the males in the seventh generation had four generations of females, in other words they inherited from their great-great great-grandfather his disease, carried latent through all the intervening females, until it became evident in them. Had this history extended no further back than through the last five generations (a rather extensive pedigree for the average family of today) one might have cited this pedigree also as proof of the law of Lossen, that the male never transmits hemophilia. In the Appleton Swain family, reported by Pratt, although there is no confirmatory labora-

tory diagnosis, the definite mode of inheritance of a sex-linked recessive character in connection with a tendency to bleed from slight wounds makes the diagnosis fairly certain. Here 13 of the afflicted children in six different families could trace their disease to their maternal grandfather, 5 in two families to their great-grandfather, and 1 had to go back through four and 1 through five generations of females before the male ascendant was reached who had passed on to them his defect.

In *Eugenical News* in 1926 there is a family reported, although the laboratory findings are not given, in which hemophilia was transmitted through the male line four times, twice from grandfather to grandson through the mother, and twice from great-grandfather to a male descendant through two intervening females. Unfortunately the laboratory diagnosis was not made to confirm the clinical, and those who wish to adhere to the rule of Lossen may refuse to admit these cases to the category of true hemophilia.

From what we know of sex-linked recessive diseases, we can feel safe in laying down the following rules for the transmission of hemophilia. These are not to be regarded as any new formulation, but rather as a restatement for the benefit of those who have been inquiring concerning the transmission of hemophilia, and who have been led astray by the old rules laid down by Lossen, together with some others that have accumulated since his time.

Summary. 1. A man afflicted with hemophilia will have no children showing this disease, provided that he marries a normal woman who is not a carrier. (Mating 2.)

2. The sons of such a man will not only be normal themselves, but they cannot transmit the defect to their descendants. (Mating 2.)

3. The daughters of such a man will be outwardly normal, but they will *all* be carriers of the defect (Mating 2), liable to give it as an evident disease to half their sons. (Mating 3.)

4. Half the daughters of a woman who is a carrier of hemophilia are apt to be carriers themselves, transmitting the defect, as their mothers did, to half their sons as an evident defect, and to half their daughters who will be carriers in their turn. Half the daughters and half the sons of a woman who is a carrier are apt to be normal. (Mating 3.)

5. Theoretically it is possible for a woman to show hemophilia as a disease, provided that she had a father who showed the disease and a mother who was either a carrier or a hemophilic herself. (Matings 4 and 6.) This may be impossible of realization, for the presence of a double quantity of the defect may act as a lethal factor inhibiting the development of the embryo. Such lethal factors are known in some other forms of life. Hess has suggested that hemorrhagic purpura may be the form which hemophilia takes in the female, since he found the former occurring in the sisters of hemophilic males.

6. If there were a woman with hemophilia, *all* her sons would exhibit the disease. (Matings 5 and 6.)

7. The only persons in a hemophilic family who can marry with impunity, are the unaffected males and their descendants.

8. All daughters of hemophilic males are carriers, (Mating 2) and should not reproduce. Since, in a family in which hemophilia is known to exist it is impossible to tell which women are carriers and which are free from the latent defect until they reproduce, it is advisable for all women in such a family to refrain from having children. Although this excludes some normal women from reproducing, it is the only safe rule to insure the elimination of the defect.

9. Hemophilia is a disease so tragic in its effects, that it is essential for those who bear the taint in their family to know what are the possibilities of their passing it on. To allow the statement to go unchallenged that it is impossible for a hemophilic male ever to have hemophilic descendants is to spread still further the taint which crops up here and there to snuff out the life of some child.

BIBLIOGRAPHY.

Bulloch, W., and Fildes, P.: Hemophilia, Treasury of Human Inheritance, 1911, **1**, 15.

Davidson, E. C., and McQuarrie, I.: Hemophilia, Three Cases, Johns Hopkins Hosp. Bull., 1925, **36**, 343.

Hess, A. F.: The Blood and Bloodvessels in Hemophilia and Other Hemorrhagic Diseases, Arch. Int. Med., 1916, **17**, 203.

Klug, W. J.: Ueber die Kirchheimer Bluterfamilien (Mampel), Deutsch. Ztschr. f. Chir., 1926, **199**, 145.

Legg, W.: Report on Hemophilia with a Note on the Hereditary Descent of Color Blindness, St. Bartholomew's Hosp. Rep., 1881, **17**, 303.

Lloyd, B. L.: Actual Pedigree of Hemophilia, Eugenical News, 1926, **11**, 170.

Lossen, H.: Die Bluterfamilie Mampel bei Heidelberg, Deutsch. Ztschr. f. Chir., 1877, **7**, 358.

Pratt, J. H.: Purpura and Hemophilia, Osler and McCrae's Modern Medicine, 1913, **4**, 717.

Nissé, B. S.: Ann. Eugenics, 1927, **2**. 25–40.

Appendix. After the above article had been submitted for publication, the author saw an abstract, published in the September issue of the *Eugenical News*, concerning an article by B. S. Nissé dealing with heredity in hemophilia, which had appeared in the *Annals of Eugenics*, 1927, **2**, 25 to 40. After much difficulty the original article was obtained, and Nissé's conclusions are here given. It will be remembered that Bulloch and Fildes rejected those cases of so-called hemophilia in which transmission through the male had occurred, explaining them as due to incorrect diagnosis, or to transmission through a carrier mother. They state (p. 169) "Transmission in any other way than through unaffected females has not been recorded in any recent publication," and again (p. 185), "Second, males in earlier generations of a pedigree are wrongly diagnosed as bleeders with the result that bleeder descendants are presumed to have inherited the disease from such males, while in reality the line of inheritance passed out of the family through the maternal side." "It must be pointed out that these instances of propagation through the male belong to the past."

Although Nissé cites these families collected by Bulloch and Fildes, he appears to be under the impression that these authors had fully accepted them as cases of true hemophilia, and so supporting the idea of transmission through the male. This I believe to be an erroneous interpretation of their conclusions, and McCrae's quotation of their ideas is in agreement

with mine, for he says that Bulloch and Fildes conclude that transmission never occurs through the male line (*Osler's Principles and Practice of Medicine*, tenth edition, 1925, p. 767). Nissé, after quoting these cases which he says support the law of Nasse, adds a new pedigree which further validates the idea that transmission does occur through the male, if he live long enough to propagate. In his pedigree, a male transmitted to two grandsons through two daughters, and another male, his brother, to one grandson through his daughter.

The other cases which have been used to prove inheritance through the male line have not been confirmed as true cases of hemophilia by laboratory diagnosis. This defect Nissé remedies by giving the coagulation time of two of his cases and the coagulation time and platelet count on a third. These figures are as follows: Four minutes thirty-five seconds coagulation time on the first case; six and a half minutes on the second; nine minutes on the third. The last patient showed a count of 87,400 platelets per cubic millimeter. These figures make us wonder if Nissé was really dealing with hemophilia.

McCrae and Hess state that in hemophilia the platelet count is normal but it is reduced in purpura, while the coagulation time is normal in purpura but much prolonged in hemophilia. The normal platelet count is 225,000 to 250,000 per cubic millimeter, and the normal coagulation time shows wide variations depending upon the time of the day at which the blood was drawn, the part of the body from which it was taken, the temperature of the room, and the method used in its estimation (*Emerson's Clinical Diagnosis*, 1921). The figures given by Nissé, therefore, appear to be more in agreement with a diagnosis of purpura than of hemophilia. McCrae states that cases of purpura are sometimes found in hemophiliac families. On the other hand, the type of inheritance conforms to that found in hemophilia. Is it possible that the laboratory diagnosis of these two conditions is not so clearcut as was supposed, and that we may find cases which fit with absolute precision into neither category; or is it possible that in some families purpura is a definite sex-linked recessive defect?

Although Nissé's cases do not lend such indubitable support to my conclusions as I had hoped, he feels that they lend strong evidence to the support of Nasse's law. Whether they can be classed as true hemophilia and so strengthen the conclusions which I have stated in my paper on the basis of the theoretical knowledge of inheritance of sex-linked recessive diseases, I am not sure, but if all cases of hemophilia are investigated from the laboratory as well as the genealogic standpoint, my statement that hemophilic males *can* transmit the disease to their daughters' sons will ultimately find verification.

PNEUMONIA IN A CASE OF CHRONIC LYMPHATIC LEUKEMIA.

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and
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Recent literature contains scanty information regarding the influence of complicating diseases upon leukemia. In 1904, Dock[1] reviewed the cases previously reported and described one of his

own. The infections in his review were typhoid fever, pneumonia, and a variety of suppurative conditions. In 20 of the 23 cases, a decrease in the total leukocytes was reported and in 11 of these the count approached normal numbers. In some cases the percentage of polymorphonuclear leukocytes was increased as a result of the infection. Enlarged organs associated with the leukemia, such as the liver, spleen, and lymph nodes, decreased in size during the infection.

Five cases of lobar pneumonia that have been described agree in general with the above findings.[2, 3, 4, 5, 6] One of these recovered, as did our case, and is said by Grawitz[2] to have had an initial fall, then a rise of the total leukocyte count with no change in the differential count. Thorsch[3] reports occasional differential counts, but daily total leukocyte counts on a case of chronic lymphatic leukemia which died on the sixth day of lobar pneumonia. He found an initial fall at the expense of the lymphocytes then a rise of both polymorphonuclears and lymphocytes to a maximum.

Case History. E. N., an Irishman by birth, aged forty-nine years, a laborer, was admitted to the Second Medical Division of Bellevue Hospital on April 1, 1927, and discharged on May 2, 1927.

He complained of a sudden chill six hours before admission, followed by pain in the right chest on coughing, and weakness.

Past History. Malaria twenty years previously; deafness of the right ear for a somewhat longer period; pneumonia ten years before; slight chronic cough for an indefinite period; he denied venereal infection, but admitted the habitual use of alcohol, especially whisky.

For the past year, he had noticed a slight but definite increasing weakness. He had also in the same period noticed small lumps on the back of his neck, which appeared to vary in size from time to time.

Physical Examination. On admission, he appeared of medium height, acutely ill; coughing. His pupils were irregular, nearly fixed to light and unequal. The nasal septum was perforated. The lungs showed definite signs of consolidation of the right upper lobe. His sputum was tenacious, the color of prune juice; temperature was 105° F.; respirations moderately rapid, and blood pressure; systolic, 90; diastolic, 58.

The course was that of a severe pneumonia. During the first three days a gradual fall in temperature to 100° occurred with apparent improvement, then a rise to 103° was accompanied by toxemia, further chills moderate distention, vomiting on the sixth day, jaundice and delirium on the ninth day. Signs of consolidation in the right lower lobe and increase in the size of the spleen so as to be palpable 3 cm. below the costal margin were noted on the ninth day. Temperature fell to normal on the eleventh day with general improvement. During convalescence in the hospital lymph nodes became palpable in the posterior cervical chain, and the spleen remained palpable. The signs of consolidation in the right apex persisted to time of discharge. Roentgenogram of the chest on the twenty-fifth day showed evidence of lobar pneumonia of the right lung and a possible chronic fibrosed pulmonary tuberculosis at the apices. The Wassermann test was negative three times. He regained strength slowly and was sent to a convalescent home in the country for one month.

The possibility of leukemia was suspected, because of the blood count, in the first two or three days of the pneumonia. A thorough examination at this time failed to show the presence of enlarged lymph nodes or spleen.

The history of former enlarged cervical nodes, gradual development of weakness, and the further progress of the case confirmed this opinion.

One hundred and fourteen days after the onset of the pneumonia the patient had returned to work following a month in a convalescent home. His only symptoms were a slight cough at night and occasional feeling of weakness. The spleen was palpable; slightly enlarged, firm discrete lymph nodes were present on both sides of the neck and in the left axilla. The chest showed no abnormal physical signs except for harsh breath sounds at the right apex. Roentgen ray showed irregular consolidation of the right upper lobe with thickened pleura, and some interlobular plastic pleurisy on the right side. The blood count showed:

Red blood cells, 4,000,000; hemoglobin, 70 per cent; leukocytes, 49,500 per c.mm.; polymorphonuclears, 22.4 per cent; lymphocytes, 74.4 per cent; monocytes, 3 per cent; myelocytes, 0.2 per cent.

Hematologic Findings. Total and differential leukocyte counts were performed daily during the disease. The percentage differential count was obtained by examining 500 successive leukocytes seen on stained cover-glass films. The total number of each type of cell per cubic millimeter were calculated from the total leukocyte count and percentages. On the chart the total leukocytes and the total number of lymphocytes and polymorphonuclears per cubic millimeters are plotted in the form of curves.

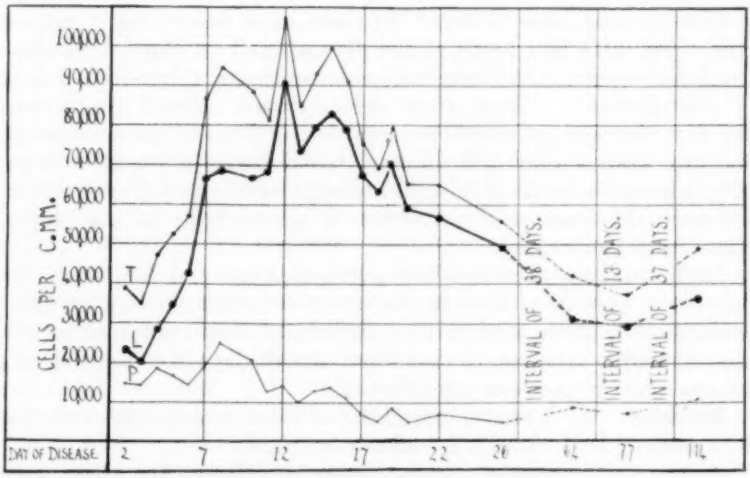
It will be seen from the chart that the leukocytes had reached practically constant numbers when examined, more than two months after the onset of the pneumonia. The average of the last three counts, performed at intervals of thirteen days and thirty-seven days, is in round numbers: Total leukocytes, 43,000 per c.mm.; lymphocytes, 32,000 per c.mm.; polymorphonuclears, 9000 per c.mm. It will be convenient to refer to these numbers as the "constant count." If we compare the changes which occurred during the pneumonia with the constant count the following points are noted:

The total leukocyte count commenced at about the level of the constant count; they increased rapidly during the first eight days to 94,000 per c.mm., and thereafter varied between 70,000 and 107,000 per c.mm. until the twentieth day, when they commenced to decrease. The increase in total leukocytes is seen to be due chiefly to an increase in the lymphocytes. These cells formed 60.6 per cent of the total leukocytes on the first examination and reached a maximum percentage of 90.2 per cent on the twentieth day. The chart shows that the lymphocytes were decreased in total numbers, compared with the constant count, during the first three days of pneumonia; but they rapidly increased, later reaching a maximum of 91,000 per c.mm. on the twelfth day. During convalescence they gradually decreased to reach the constant count, about 32,000 per c.mm.

It will be seen from the chart, that in spite of the abnormal differential count, a definite polymorphonuclear leukocytosis was present during the acute stage of the disease. There were 15,000

polymorphonuclears per c.mm. on the first examination; they increased to 25,000 per c.mm. on the eighth day, and thereafter gradually fell to within normal limits.

The monocyte count cannot be regarded as very accurate, as the percentage of these cells during the acute stage of the disease was never above 2, and was often below 1; but the counts indicate that



T = Total leukocytes per c.mm.
P = Total polymorphonuclears per c.mm.
L = Total lymphocytes per c.mm.

these cells rose from normal numbers in the beginning to a maximum of 1900 per c.mm. on the twelfth day, and then soon fell to normal numbers.

Eosinophils were not seen in any count until the seventeenth day. Thereafter they were present in low numbers on most occasions.

The blood counts show that in this case the bone marrow was able to produce a high polymorphonuclear leukocytosis as a result of the infection. The rapid and great increase in the lymphocytes indicates a hyperactivity of the lymphatic apparatus. The highest lymphocyte counts appeared at about the time when there is an increase in the lymphocytes in normal cases of pneumonia. The difference is rather in the degree of this lymphocyte response.

Serologic Findings. Immune reactions in the presence of leukemia are discussed by Ordway and Gorham.[7] The work which they review and subsequent work has been done almost entirely with typhoid and paratyphoid infection and immunization. In general, it has been found that the opsonic and phagocytic powers of leukemic blood are feeble and that antibodies such as agglutinins are usually absent.

In the case described above pneumococcus Type I was isolated from the sputum on two occasions and from the blood stream on five successive days the third to the seventh of the disease. The bacterial count in the blood was low, not exceeding 4 per cc. at any time.

Tests of the protective power of the patient's serum for mice inoculated with pneumococcus Type I were made. The serum specimens used were obtained on three days before defervescence (the third, fifth and ninth of the disease) and on three days after the defervescence (the fourteenth, nineteenth and thirty-fourth days of the disease). Those after defervescence showed protection, the first two against 10,000 minimal lethal doses of pneumococcus, the last against only 100 minimal lethal doses of pneumococcus. This approximates the finding in uncomplicated cases of pneumonia, although the amount of protection is not as large as may sometimes be demonstrated.

Agglutinins are found in low concentrations and frequently for only short periods of time in the serum of patients following lobar pneumonia. Their absence in specimens of serum obtained on the eighth, tenth, seventeenth and thirty-fourth days does not indicate an abnormal response to the infection.

Summary. 1. A case is presented of lobar pneumonia occurring in a patient with chronic lymphatic leukemia.

2. The daily variations in the leukocytes during the acute stage of the pneumonia, and the condition of the blood after a long convalescence are described.

3. It was found that an absolute polymorphonuclear leukocytosis occurred although the relative count was low. The lymphocytes increased rapidly to a high figure during the first week, and decreased very slowly in the weeks of convalescence.

4. Specimens of blood serum taken after recovery showed the presence of protective antibodies in moderate amount for the homologous organism. No agglutinins were found.

BIBLIOGRAPHY.

1. Dock, George: Investigations in Leukemia, Am. J. Med. Sci., 1904, **127**, 563.
2. Grawitz, E.: Klinische Pathologie des Blutes, Berlin, Otto Enslin, 1902, p. 339.
3. Thorsch, Edmund: A Contribution to the Study of the Effect of Acute Infections upon Leukemia, Wien. klin. Wchnschr., 1896, **20**, 395.
4. Hart, T. S.: Chronic Lymphatic Leukemia Complicated by Pneumonia, N. Y. and Phila. Med. J., 1903, **78**, 224.
5. Bickhardt, Kurt: Of the Morphological Character of Exudates in Cases of Leukemia, Fol. Hemat., 1925, **32**, 83.
6. Froelich, E.: An Unusual Case of Pseudoleukemia, Wien. med. Wchnschr., 1893, No. 7, 286.
7. Ordway, T., and Gorham, L., Whittington: Leukemia, Oxford Medicine, vol. **11**, Part 11, p. 727, Oxford University Press, American Branch, New York City, 1920.

THE BASAL METABOLISM IN CHRONIC LYMPHATIC LEUKEMIA.

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Two nonfebrile conditions are preëminently associated with an increased metabolic activity, namely, hyperthyroidism and the leukemias. An increased or abnormal thyroid secretion is assumed to be the underlying factor in the first, while the cause or causes of the elevated energy exchange in the latter is yet to be definitely determined. There is a further similarity between these diseases in that irradiation with Roentgen rays or radon is usually followed by a drop in the heat production. In myelogenous and lymphatic leukemia the levels of the leukocyte count and of the different sorts of immature white blood cells have been considered useful criteria in determining treatment by such irradiation. The height of the basal metabolism in hyperthyroidism aids in establishing the degree of disease activity and when properly determined and evaluated it also helps govern the therapy in the different types of leukemia. It is the application of such knowledge to the treatment of patients with chronic lymphatic leukemia that is discussed in this paper, together with observations concerning the basal metabolism and its relationship to the state of the blood.

The first report of an increased energy exchange in leukemia was made by Bohland[1] in 1893. He studied 3 cases, particularly because of the anemia, which he sought to associate with an altered respiratory exchange. In 1906, Magnus-Levy[2] summarized the available knowledge of the respiratory metabolism in the leukemias by stating that a rise in the basal metabolism sometimes occurred, but it was usually to be found at the upper limit of normal. The literature on the basal metabolism in the leukemias concerns myelogenous leukemia for the most part and this aspect has been reviewed and discussed recently by Riddle and Sturgis.[3] Minot and Isaacs,[4] on the other hand, have studied the effect of Roentgen rays and radon irradiation in patients with lymphatic leukemia and have noted a subsequent lowering in the basal metabolic rate as well as a decrease in the leukocyte count and symptoms due to increased metabolism.

Material and Methods. The basal metabolism and state of the blood has been studied in 31 patients with chronic lymphatic leukemia, upon whom 244 metabolic determinations were made. These observations were made not only before and after treatment with

Roentgen rays and radon, but also during the course of the disease. Four of these patients were the subjects of daily intensive studies. The data are presented from two standpoints: (1) A statistical study of the basal metabolism and the formed elements of the blood; (2) similar daily studies on selected cases. Dr. G. R. Minot anticipated this intensive study on the basal metabolism of chronic lymphatic leukemia and thus some of the data at our disposal were collected prior to our investigations, particularly by Dr. J. Hitchcock. Observations on patients whose lymphoid tissue showed a pathologic picture, but who at no time disclosed a blood picture of lymphatic leukemia, that is, cases of "pseudo-leukemia" are excluded from this series. However, patients in whom an aleuokocythemic blood picture was presented at one time and a leukemic picture at another are included.

The patients were studied in the postabsorptive condition, twelve hours or more after the last ingestion of food. The metabolism determinations were made in the usual manner on a Collins-Benedict apparatus. During several of the observations an elevated temperature was found and proper correction for this was made by deducting 7.2 per cent for each degree (F.) of fever.[5] In most cases, 5 or more metabolic determinations were made on each person, the greatest number of observations on any one being 37, while there was only one determination made on each of four individuals. The daily studies include control periods of one to four days before Roentgen ray or radon irradiation.

Total and differential white blood cell and erythrocyte counts, together with the determination of the percentage of hemoglobin and estimations of the number of blood platelets from very carefully prepared stained blood smears were made in almost every case. In a few instances the blood platelets were counted by means of hemocytometer and pipette. The examination of the blood was made at the time of the metabolism determination except in a few of the earlier observations. The distinction between small, large and immature lymphocytes was noted to determine whether or not there was any relationship between the age of the lymphocytes and the height of the metabolic rate. This was done particularly because the numbers of immature cells in myelogenous leukemia seem to bear a direct relation to the amount of increase of the basal metabolic rate as shown by Gunderson[6] and also by Riddle and Sturgis.[3]

I. **The Statistical Study of the Basal Metabolism and State of the Blood. A. The Basal Metabolism and Leukocyte Level Before and After Irradiation.** Thirty-two of the 244 observations were made upon 18 patients before any irradiation was given. These results are shown in Table I. With but one exception the metabolic rate was elevated, the majority showing an increase from 10 to 45 per cent above the average normal level. The highest rate observed in these nonirradiated cases was + 68 per cent. It appears, there-

fore, that when lymphatic leukemia has progressed far enough to cause symptoms sufficient to make the affected individual seek medical aid at a hospital of this type,* the basal metabolism has reached a level above normal.

TABLE I.—THE RANGE OF BASAL METABOLIC RATE, BASAL PULSE RATE AND WHITE BLOOD CELL COUNT IN UNTREATED CASES OF LYMPHATIC LEUKEMIA.

Range of basal metabolic rate.	Number of cases.	Number of determinations.	Average basal pulse rate.	Range of white blood cell count, thousands per c.mm.
0 to + 9	1	1	76	42
+10 to +19	5	7	70	35 to 539
+20 to +29	3	7	75	33 to 597
+30 to +39	3	9	87	21 to 115
+40 to +49	4	5	88	57 to 123
+50 to +59	1	2	86	72 to 129
+60 to +69	1	1	94	36

TABLE II.—THE RANGE OF BASAL METABOLIC RATE, BASAL PULSE RATE AND WHITE BLOOD CELL COUNT IN TREATED AND UNTREATED CASES OF LYMPHATIC LEUKEMIA.

Range of basa metabolic rate.	Number of determinations.	Average basal pulse rate.	Range of white blood cell count thousands per c.mm.
−10 to − 1	10	70.6	5 to 186
0 to + 9	26	66.5	3 to 484
+10 to +19	43	70.6	2 to 544
+20 to +29	64	73.2	4 to 596
+30 to +39	41	79.7	3 to 212
+40 to +49	36	84.0	2 to 385
+50 to +59	17	85.6	3 to 379
+60 to +69	3	88.7	11 to 150
+70 to +79	2	89.0	17 to 23
+80 to +89	2	96.5	70 to 90

The complete data obtained from studies upon irradiated and nonirradiated individuals are summarized in Table II. One hundred and ninety-four of the 244 observations showed that the metabolic rate was increased from 10 to 50 per cent above the normal average. Unusually high rates were found in several instances, the highest rate observed being 83 per cent above normal. On the other hand, 36 of the determinations were within normal limits and yet the leukocyte counts in these patients varied from 2800 to 483,500 cells per c.mm. As the higher levels of metabolic activity were reached, the leukocytes did not always show high counts. Of 30 metabolic determinations upon patients whose leukocyte level was above 250,000 cells per c.mm., 23, or 77 per cent showed a rise of less than

* The patients seen in this hospital have usually been referred for treatment by outside physicians. The diagnosis of lymphatic leukemia has thus generally been made before arrival at the hospital.

30 per cent. Thus, when a group of cases is considered, it appears that there is no definite relationship between the basal metabolism and the level of the leukocytes. In each individual case, however, a general relationship does exist between these two factors and this is discussed further on.

The average basal pulse rate showed a constant increase as the heat production rose. This, Minot and Means,[7] have interpreted as a result due to the increased metabolic rate. There were wide individual variations in the pulse rate, dependent in part upon anemia and other factors. Therefore, only the association of a low basal pulse rate with a low basal metabolic rate may be considered of any significance.

Patients with lymphatic leukemia may show symptoms which are definitely associated with, and probably due to an increased metabolism. These are: an increased pulse rate; easy fatigability; usually an increased rate and volume of respiration; a sensation of warmth; an increased tolerance for cold; loss of weight; a warm, moist skin; and not uncommonly sweating. As these symptoms become more pronounced, the respiratory exchange rises. After irradiation with Roentgen ray or radon, these symptoms often lessen and even disappear when adequate treatment has been given. At the same time the basal metabolic rate drops and may return to normal after sufficient irradiation. The leukocytes may show a sudden and marked drop without any distinct decrease in the patient's symptoms and the heat production may even rise temporarily after irradiation as is illustrated in Charts III, IV, V and VI. Therefore, the basal metabolic rate is perhaps a truer indicator of the condition of the patient and is to be correlated more closely with his symptoms, than is the height of the leukocyte count. When the metabolic rate has returned to a normal level after irradiation, the patient gains in strength and in ability to resume a useful occupation and this, after all, is a criterion of beneficial treatment.

B. Relationship of the Basal Metabolic Rate to the Immature Cells. The relationship between the numbers and character of the immature white blood cells and the basal metabolic rate has been found to be less evident in lymphatic leukemia than in myelogenous leukemia. This lack of correlation may be more apparent than real, for it is more difficult to determine the degree of immaturity of the lymphocytes than of the myeloid cells. However, when there were many immature cells such as lymphoblasts, the patient was distinctly ill and the basal metabolism high. Such individuals usually have not been benefited by therapy and have soon died. Chart VI illustrates the course of a case in which the lymphoblasts varied from 8 to 20 per cent of the total leukocyte count. A fatal outcome resulted one month after the last observation and Roentgen ray irradiation caused only a temporary reduction in the metabolic rate and white blood cell count, with a quick return to their former

levels. Even when the leukocyte count was low, the immature cells persisted in the peripheral blood.

Most of the cases presented a considerable predominance of small lymphocytes over other cells in the circulating blood. There was a definite tendency for the large lymphocytes and immature lymphocytic cells to increase as the heat production rose. The percentage of lymphocytes fell markedly in some cases under Roentgen ray or radon therapy. However, a high percentage of lymphocytes may occur when the white blood cell count is either high or low, but a distinct decrease in their percentage after irradiation is more apt to be observed when the total leukocyte count is relatively low. A reversal of the percentage of lymphocytes in the blood as compared to the white blood cells derived from the bone marrow does not appear to influence the length of the disease.

C. The Relationship of the Basal Metabolic Rate to the Numbers of Blood Platelets. Decrease of the blood platelets is a characteristic feature of chronic lymphatic leukemia. Minot and Buckman[8] record a marked reduction of blood platelets when the total number of lymphocytes are excessive, the percentage of immature cells high, or the hemoglobin level low. In our cases a high metabolic rate was usually associated with a marked decrease in the blood platelets, while a low rate was found in patients where they were normal or only slightly diminished.

When the disease process encroaches upon the bone marrow, a marked reduction in the blood platelets may occur. If these elements fall to 60,000 per c.mm. or below, purpura with bleeding from the mucous membranes is apt to ensue. An increase in the immature lymphocytic cells may also occur under these circumstances and the basal metabolic rate decrease only very temporarily from high levels after Roentgen ray irradiation, as is illustrated by the data given in Chart VI.

Many patients were studied over a period of months and repeated blood examinations usually showed a shift in the number of blood platelets toward normal after proper irradiation in cases where the basal metabolic rate had returned to low levels. Usually, however, a slightly reduced number of these elements persisted, though the leukocyte counts and energy exchange were within normal limits. The basal metabolic rate almost always bore an inverse relationship to the number of blood platelets.

When many grossly immature cells are present in the blood in myelogenous leukemia, the blood platelets are usually low and the basal metabolism high. However, under varying circumstances in this disease, an increased, normal, or diminished number of blood platelets occurs and these elements often return to normal after Roentgen ray or radon treatment.[8] In lymphatic leukemia there appears to be a much less marked tendency for the blood platelets to return to normal after irradiation than in myelogenous leukemia,

probably because the bone marrow is secondarily involved in lymphatic leukemia, rather than primarily as in myelogenous leukemia.[9] But in each of these conditions an increase in the number of grossly immature cells is often accompanied by a thrombopenia and an elevation of the basal metabolism.

D. Relationship of the Basal Metabolic Rate to Anemia. In their discussion of anemia in lymphatic leukemia Minot and Isaacs[4] state: "The hemoglobin level is an important index of the state of the patient and the effect of the disease on the marrow may be indicated by the degree of anemia. When the hemoglobin is 50 per cent or below, it is rare to see much symptomatic improvement." To determine what relationship exists between the metabolic rate and anemia, three individuals in whom the hemoglobin was below

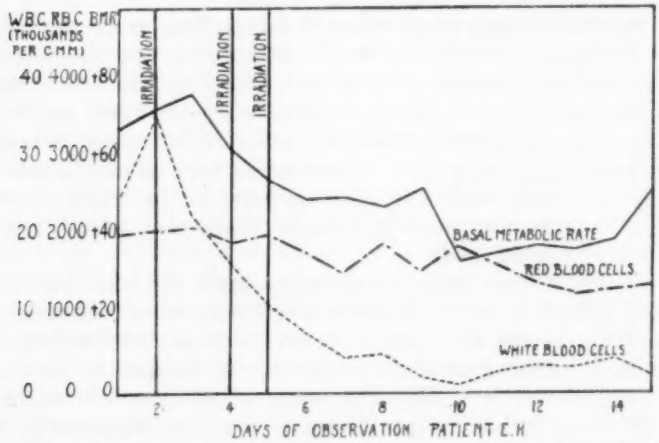

CHART I.—Basal metabolism after irradiation of a case with low red cell picture. Five hundred electrostatic units of Roentgen ray irradiation were given at each exposure.

50 per cent were studied. The results obtained in two of these patients, which are similar to the third, are shown in Charts I and II. In neither individual did the basal metabolic rate return to normal after irradiation, though some decrease in the heat production occurred. The leukocyte count continued to drop in each of the patients. After the lowest level of metabolism had been maintained for several days after Roentgen ray irradiation, a rise in the heat production occurred. In the first case the low leukocyte level and in the second the low erythrocyte count were considered contraindications to further treatment by irradiation. In both cases it is to be noted that the red blood cell count continued to decrease after the application of Roentgen rays. On the other hand, in cases where the hemoglobin percentage and the erythrocyte count were normal or only slightly reduced, there was no rapid return of an increased basal metabolism after irradiation. Chart III illustrates

such a case. Here the red blood cells were found to be in the vicinity of 4,000,000 per c.mm. and even several months later the basal metabolism remained low and the erythrocytes had increased slowly. In this case, the average basal pulse rate was 69 per minute, whereas in the 2 cases with marked anemia, the basal pulse rate varied from 88 to 100 beats per minute.

The health of another patient with severe anemia became greatly improved after Roentgen ray irradiation. However, when marked anemia occurs in lymphatic leukemia, considerable improvement in the patient's health is not the rule. The erythrocyte count does not immediately increase after intensive irradiation in this disease. At first it often decreases slightly and then rises slowly, often beginning to increase only several weeks after treatment. It appears from our studies that a normal basal metabolism is hard to obtain

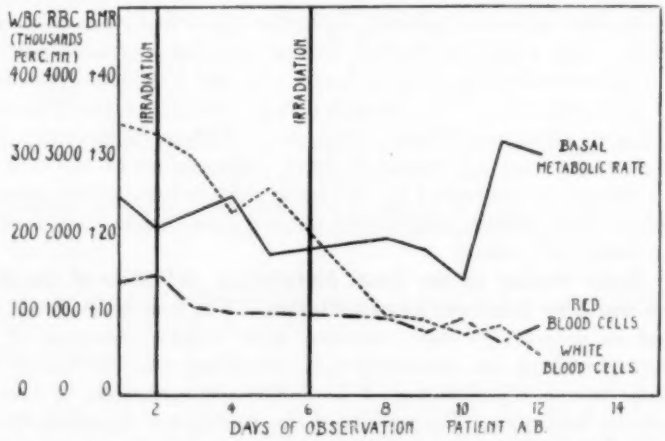

CHART II.—Basal metabolic rate after irradiation of a case with low red cell picture. Two hundred and fifty electrostatic units of Roentgen ray irradiation were given at each exposure.

where the associated anemia is severe, even though the leukocytes have reached a low level.

E. The Basal Metabolic Rate in Various Stages of Chronic Lymphatic Leukemia. No patients with lymphatic leukemia were observed when the disease was in the incipient stage, but presumably there is no increase in the heat production at such a time. However, if the disease has progressed far enough to cause obvious symptoms, the metabolic rate has increased in almost all instances above normal. At such a time the patient can be benefited by proper Roentgen ray or radon treatment. As successive courses of irradiation are given, there is a progressively less favorable reaction to the same dosage, as is shown by a study of the symptoms, the state of the blood and the basal metabolism. An increasing severity of the disease is shown particularly by the following five conditions which are associated

with an increased basal metabolism: (1) An increase in the symptoms of the patient, among which fever, due to the leukemic process, is often present. (2) A rise in the white blood cell count. (3) An increase in the number of immature lymphocytes, as well as in the degree of immaturity. (4) A reduction in the blood platelets. (5) Progressive anemia.

In the final stages of the disease the activity of the leukemic process becomes more marked and irradiation is of little benefit.

F. Discussion. It seems to us that the basal metabolism is a truer indicator of the activity of the leukemic process than is the leukocyte count. The leukocyte count may be high in one individual and low in another, yet both may have a high basal metabolism. Various authors have suggested that the white blood cell level may be influenced by the rapidity of elimination or destruction of the leukocytes. Isaacs and Danielian[10] have recently studied the excretion of leukocytes in the saliva in patients suffering from leukemia and have suggested that a leukopenia may be due to either increased elimination or decreased production of leukocytes and that any given level of white blood cells can be dependent upon varying rates of production and elimination of these cells. Any of these factors may thus account for a varying leukocyte level, independent of the activity of the disease as measured by the basal metabolism, which appears to bear a closer relationship to the patient's condition than does the white blood cell count.

II. Daily Studies on the Basal Metabolism and State of the Blood Before and After Roentgen Ray Irradiation. The four individuals who served as subjects of daily studies were selected because of the different levels of the leukocyte count in three and the fourth was studied intensively because of an active exacerbation of chronic lymphatic leukemia. The results of the studies are shown in Charts III, IV, V and VI.

Chart III illustrates the association of a comparatively low leukocyte count—30,000 cells per c.mm.—with an increased energy exchange. The patient had a slight anemia and her blood platelets were only slightly diminished. She complained primarily of symptoms due to an elevated heat production, and two Roentgen ray exposures of 500 electrostatic units each sufficed to make these symptoms disappear. The basal metabolism started to fall from + 38 directly after the first treatment and continued to do so for nine days when it became normal. The total leukocyte count fell in the same period to 2300 cells per c.mm. and the lymphocytes from 93 to 34 per cent.

Data obtained from studies upon a patient with a moderately high initial leukocyte count—75,000 cells per c.mm.—with an elevated metabolic rate are shown in Chart IV. Here a striking drop in the number of leukocytes occurred after the first irradiation of 500 electrostatic units, but not until a second application of the

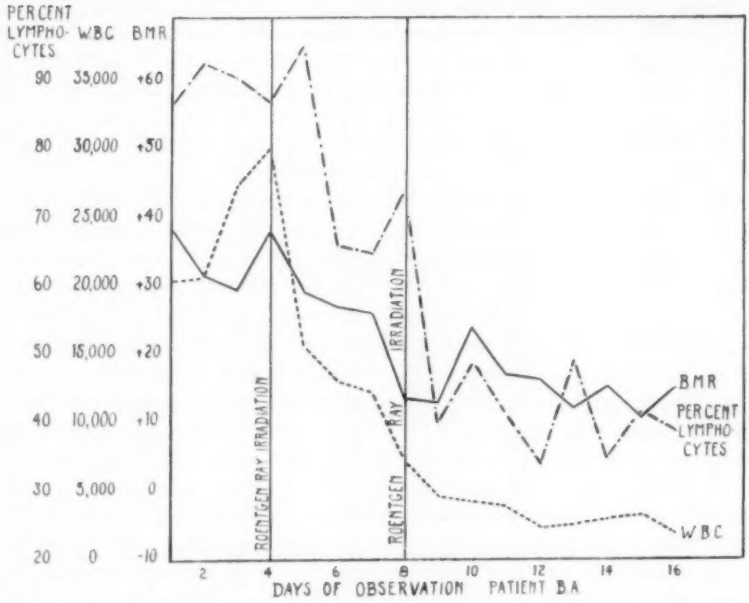

CHART III.—Basal metabolic rate after irradiation of a case with low leukocyte count. Five hundred electrostatic units of Roentgen ray irradiation were given at each exposure.

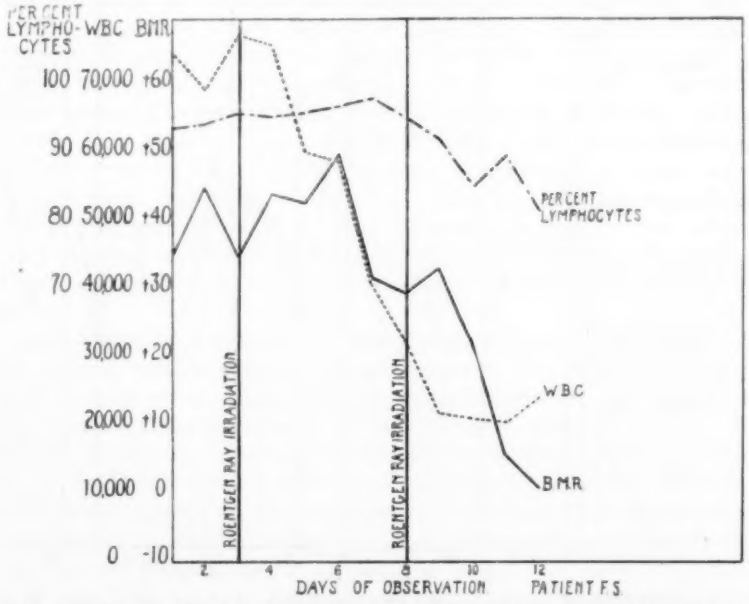

CHART IV.—Basal metabolic rate after irradiation of a case with moderately high leukocyte count. Five hundred electrostatic units of Roentgen ray irradiation were given at each exposure.

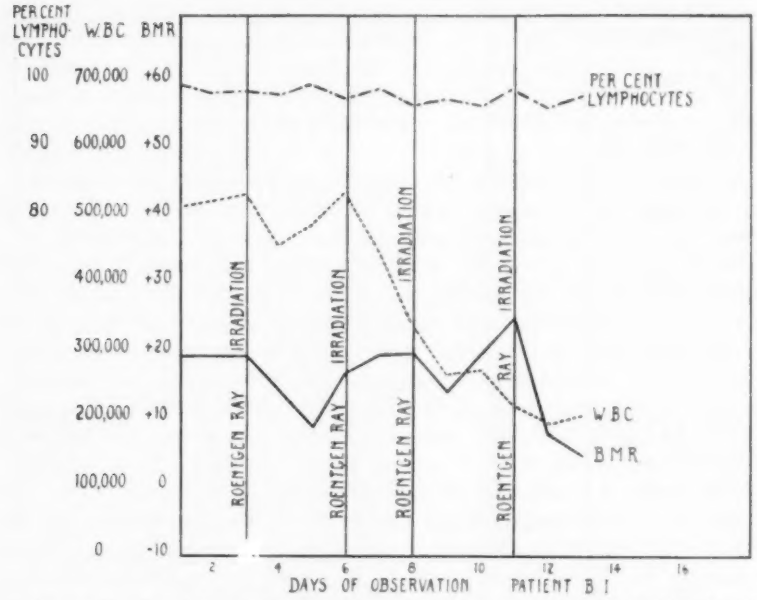

CHART V.—Basal metabolic rate after irradiation of a case with high leukocyte count. Five hundred electrostatic units of Roentgen ray irradiation were given at each exposure.

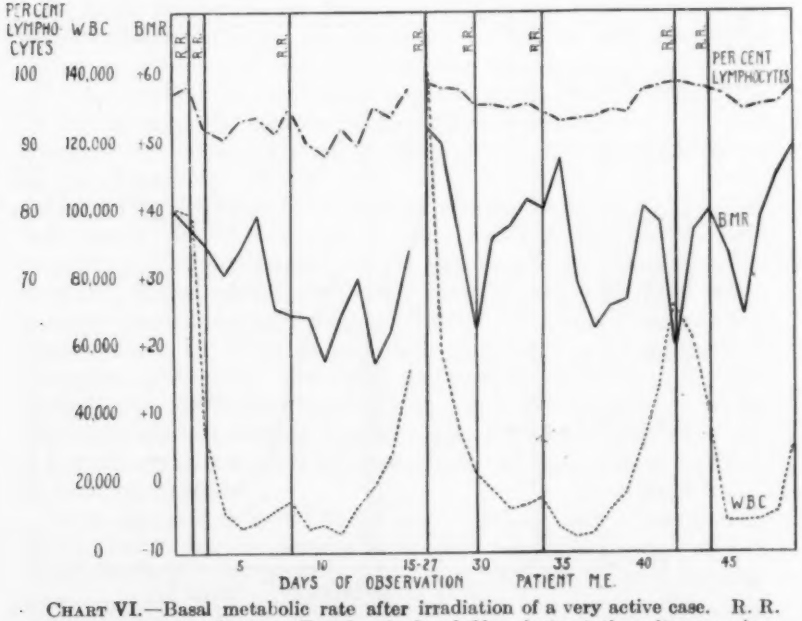

CHART VI.—Basal metabolic rate after irradiation of a very active case. R. R. = Roentgen ray irradiation. Two hundred and fifty electrostatic units were given at each exposure.

same dosage five days later did the energy exchange become normal. A third patient showed a low level of heat production combined with a high total white blood cell count when first seen by us and results of these observations are shown in Chart V. It was not until after four Roentgen ray exposures of 500 electrostatic units each had been given that the slightly elevated heat production of this patient remained normal. The leukocyte count continued to drop from a level of 500,000 cells per c.mm. before irradiation to 200,000 at the time the basal metabolism became normal. However, several weeks later the count fell to 125,000 cells per c.mm. The symptoms of increased heat production, though never severe, disappeared within nine days after therapy had been commenced.

Chart VI represents studies upon a patient with a marked activity of the disease. Not only was the basal metabolism elevated, but the formed elements of the blood gave evidence of the severity of the disease as noted above. Eight Roentgen ray exposures of 250 electrostatic units each were given in spite of the obvious involvement of the bone marrow. The number of white blood cells fell, but the immature lymphocytes persisted in the same percentage as before. The basal metabolic rate never reached normal, nor was the patient in any way symptomatically benefited. A few days after the last Roentgen ray application the leukocyte count and heat production rose again to former high levels.

Riddle and Sturgis[3] have noted a rise in the basal metabolism in myelogenous leukemia coincident with a fall in the leukocyte count within a period of several days after irradiation. This also has been found to be true in lymphatic leukemia as will be noted upon examination of any of the accompanying charts. The same observers often noted a temporary but distinct rise in the leukocyte count during this period which preceded a general drop in the number of leukocytes. This is in direct contrast to the findings in our cases of lymphatic leukemia, where such a rise in the leukocytes was never demonstrable. After these temporary changes have taken place, there is a fall in both the number of white blood cells and in the basal metabolism, suggesting a general relationship of one to the other.

Indications for Roentgen Ray and Radon Therapy. Treatment of the patient with lymphatic leukemia is not to be limited to irradiation therapy alone. This form of therapy, however, does improve the patient symptomatically for a time, and when the disease is not too far advanced he may be able to resume his normal activities until the disease process once more gains the upper hand. Experience has suggested to us that there are certain definite indications for irradiation when Roentgen rays or radon can be of benefit in this disease, namely:

I. Indications for Treatment Directed Toward the Patient's Condition in General. A. When symptoms of elevated

energy exchange occur or when the basal metabolism is elevated above normal, provided irradiation is not contraindicated because of recent exposure to Roentgen rays or radon. As the symptoms and the elevated basal metabolic rate may be associated with few or many circulating white blood cells the determination of the energy exchange serves as a means to govern the extent of therapy, particularly when the leukocyte count is low.

B. When the white blood corpuscles are 100,000 or more per c.mm. Such an elevated leukocyte count may occur with a heightened basal metabolism or with symptoms due to pressure from diseased tissue and either of these indicate that therapy is desirable. It is a mistake to treat the white blood cell count only; the patient and not abnormal physical signs must be treated. At times, however, a leukocyte count of 100,000 cells or more per c.mm. may occur when the energy exchange is normal and as it seems unwise to permit so many cells to be in the circulation, therapy for their reduction appears to be desirable.

II. Indications for Treatment Directed Toward a Local Condition. When pressure from diseased tissue causes symptoms. In the neck the enlarged lymph nodes may interfere with deglutition, may obstruct breathing, or may cause obstruction to the blood or lymph flow. In the thorax, increase of lymphoid tissue may press upon the trachea, blood and lymph channels, and surrounding structures, causing undesirable symptoms. Lymphoid tissue enlargement may obstruct the venous or lymph channels in the pelvic region so that edema of the lower extremities may cause considerable discomfort and disordered function. To a less extent, this is true of the axillary regions. At times the spleen may enlarge to a considerable extent and symptoms due to its size may result. Enlargement of the lymphoid tissue within the abdomen may lead to many sorts of symptoms[11] and these may be decreased by appropriate therapy.

Contraindications for Roentgen Ray or Radon Therapy. Roentgen rays or radon should not be administered to patients simply because they have chronic lymphatic leukemia, or, when they have this disease, simply because the white blood cell count is elevated. The routine treatment of these patients by such irradiation is to be decried when the definite indications for treatment given above are not present. On the other hand, when the patients are obviously ill there are certain conditions when the application of Roentgen rays or radon can produce little or no benefit, and as such may be considered contraindicated, namely: (1) When the bone marrow is markedly involved in the disease process, so that anemia and thrombopenia are pronounced; (2) when the circulating blood contains large numbers of very immature lymphocytes; (3) when recent adequate therapy has not benefited the patient.

The conditions that indicate caution in the use of Roentgen ray

or radon therapy apply, of course, to lymphatic leukemia as well. For example, exposure must not be given too often over the same area. A suberythema dose of 1000 to 1200 electrostatic units should not be applied to the same region, more often than every five or six weeks. When diabetes mellitus or advanced nephritis are present, care should be taken in the application of such treatment.

Leukopenia has often been considered a contraindication to irradiation therapy. There is no doubt but that patients with lymphatic leukemia who have a leukopenia should be treated cautiously, but when a low leukocyte count and an elevated basal metabolism or symptoms due to pressure of diseased tissue are present, full doses of Roentgen rays or radon can be given with safety and benefit.

Summary and Conclusions. The study of the basal metabolism and the formed elements of the blood in 31 cases of chronic lymphatic leukemia leads to the following conclusions:

1. The basal metabolic rate in this disease is elevated when the leukemic process has progressed far enough to cause other than local symptoms.

2. The rise in the basal metabolic rate is not closely related to the height of the leukocyte count, when a group of cases is considered. In individual cases, the basal metabolism and leukocyte count vary simultaneously in a similar manner after Roentgen ray or radon application.

3. A dose of 250 or 500 electrostatic units of Roentgen rays often produces a marked decrease in the leukocyte count. A short, transitory rise in the basal metabolism is often found within three days after the application of such treatment.

4. The elevation of the basal metabolic rate appears to be less labile than the leukocyte count and it is more directly comparable with the patient's symptoms than with the white blood cell count.

5. The presence of considerable numbers of distinctly immature lymphocytes is usually associated with an increased energy exchange. When irradiation causes but slight or no decrease in the numbers of these cells, the basal metabolism usually does not fall to normal, and it soon returns to its former level.

6. The numbers of blood platelets tend to bear an inverse relationship to the basal metabolic rate.

7. Individuals with marked anemia appear to maintain a higher level of metabolic activity than those without this disorder.

8. The determination of the basal metabolic rate is a valuable guide in the treatment of patients by means of Roentgen rays or radon, particularly when the white blood cell count is low.

9. Patients with lymphatic leukemia should be treated with Roentgen rays or radon only when there are adequate reasons for doing so.

NOTE.—The authors wish to gratefully acknowledge the assistance of Miss Geneva A. Daland and Miss Margaret Evans in making some of the blood and metabolism observations.

BIBLIOGRAPHY.

1. Bohland, K.: Ueber den respiratorischen Gaswechsel bei verschiedenen Formen der Anämie, Berl. klin. Wchnschr., 1893, **30**, 417.
2. Magnus-Levy, A.: Der Einfluss von Krankheiten auf den Energiehaushalt im Ruhestand, Ztschr. f. klin. Med., 1906, **60**, 177.
3. Riddle, M. C. and Sturgis, C. C.: Basal Metabolism in Chronic Myelogenous Leukemia, Arch. Int. Med., 1927, **39**, 255.
4. Minot, G. R. and Isaacs, R.: Lymphatic Leukemia; Age Incidence, Duration and Benefit Derived from Irradiation, Boston Med. and Surg. J., 1924, **191**, 1.
5. Du Bois, E. F.: Basal Metabolism in Health and Disease, ed. 1, Philadelphia, Lea & Febiger, 1924, p. 330.
6. Gunderson, A. H.: The Basal Metabolism in Myelogenous Leukemia and its Relation to the Blood Findings, Boston Med. and Surg. J., 1921, **185**, 785.
7. Minot, G. R. and Means, J. H.: The Metabolism-pulse Ratio in Exophthalmic Goiter and in Leukemia, Arch. Int. Med., 1924, **33**, 576.
8. Minot, G. R. and Buckman, T. E.: The Blood Platelets in the Leukemias, Am. J. Med. Sci., 1925, **169**, 477.
9. Piney, A.: The Neoplastic Nature of the Leukemic Process, Am. J. Med. Sci., 1925, **169**, 691.
10. Isaacs, R. and Danielian, A. C.: Maintenance of Leukocyte Level and Changes during Irradiation. A Study of the White Blood Corpuscles Appearing in the Saliva and their Relation to Those in the Blood, Am. J. Med. Sci., 1927, **174**, 70.
11. Minot, G. R. and Isaacs, R.: Lymphoblastoma. Aspects Concerning Abdominal Lesions, Especially their Production of Early Symptoms, Am. J. Med. Sci., 1926, **172**, 157.

PRIMITIVE HUMAN HEARTS.

Cor "Biloculare" and Triloculare; Report of Cases.

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Developmental defects of the human organism are primarily of interest in that they may shed light upon various embryologic and evolutional phenomena. Severe cardiac malformations especially are often dismissed as mere curiosities and incompatible with life, but it has been shown repeatedly that these anomalies may claim even the attention of the clinician. In the museum of King's College Hospital may be found the heart of a thirteen-year-old boy which is said to consist of a single atrium and a single ventricle.[1] One of the cases herein reported was that of an individual who lived to the age of fifteen years, was economically self-supporting and worked as a maid until three weeks before her death from meningitis. The other case was functionally a two-chambered heart and coëxisted with complete transposition of viscera, including a very primitive arrangement of the transposed great vessels.

Case Reports. CASE I.—M. B, a mulatto girl, aged fifteen years, unmarried, was admitted to the medical service March 5, 1925. She was unconscious on admission and remained so until her death twenty-seven hours later. A brief history was obtained from her mother.

The patient was born at full term and delivery was normal. Nothing unusual was noticed at birth and the child seemed to be in good health during infancy. A definite clubbing of the fingers, however, was early noted. During childhood, she often complained of dyspnea on exertion and was unable to play strenuously with other children.

The girl's health had been very good and she was attending to her usual duties three weeks before admission to the hospital when she became ill with a severe headache, which, however, did not compel her to go to bed. Two weeks later she began to have fever and occasional nausea and vomiting. This, with an increase in the severity of the headaches, confined her to bed. She grew rapidly worse and on the day before admission became unconscious and incontinent of urine and feces. She was admitted with a diagnosis of acute meningitis, old endocarditis, and an undiagnosed irregularity of the heart.

The patient was well developed and nourished, quite mature in appearance and apparently about twenty years of age. She lay in dorsal decubitus with the eyes fixed in a vacant stare and could not be aroused. The skin temperature was slightly elevated.

The pupils were equally contracted and reacted to neither light nor distance. There was a slight increase in lacrimation and the conjunctivæ were moderately injected. Pronounced bilateral exophthalmos was present. Ophthalmoscopic examination disclosed bilateral papilledema, most marked in the left eye.

The neck was rigid and drawn to the right.

The thorax was symmetrical, expansion equal and of normal type. The breasts were those of a mature woman and normal. The extreme dyspnea and hypernea, 102 per minute, made examination unsatisfactory, but coarse mucous râles were heard throughout both lungs. No impairment of resonance could be elicited.

The apex beat was diffuse and thrusting, of maximum intensity in the sixth intercostal space 10 cm. to the left of the midsternal line. On account of the rapid rate of the heart, 204 beats per minute, auscultation was almost impossible, but there seemed to be a continuous murmur, especially loud over the pulmonic area. The radial pulse was 120 per minute and very weak. The irregularity mentioned by the admitting officer was not discernible. Blood pressure was 80 mm. systolic and 0 mm. diastolic.

The abdomen was normal except for slight enlargement of the liver. The external genitalia were those of maturity and well developed.

Clubbing of the fingers and toes with curving of the nails was very marked and terminal cyanosis extreme.

The patellar reflexes were exaggerated, the abdominals absent and Babinski sign bilaterally positive. Ankle clonus was well sustained on both sides and Brudzinski and Kernig signs strongly positive.

Examination of the blood and urine revealed nothing of importance except a polymorphonuclear leukocytosis and a trace of albumin. There was no polycythemia. Wassermann reaction was negative.

Spinal-fluid examination showed cloudy fluid under high pressure. The globulin content was increased and the cell count was 250, 69 per cent being polymorphonuclear leukocytes. Wassermann reaction, colloidal-gold test, culture and examination of a stained smear were all negative.

The patient remained comatose and incontinent of urine and feces. The temperature ranged between 100.4° and 103° F. The apex rate varied from 204 to 208 and the radial pulse from 120 to 140 beats per minute. She grew rapidly weaker and died twenty-seven hours after admission to the hospital.

NECROPSY. The peritoneal cavity revealed an arrested stage of rotation of the entire colon, which possessed an abundant mesocolon and was quite mobile.

Two lobes were present in each atypically fissured lung.

The pericardial cavity contained 40 cc. of straw-colored fluid and showed an old scar over the aorta.

The heart (Fig. 1) was of an unusual globular shape and quite large weighing 820 gm. The apex was rounded and lay to the left of the midsternal line. A large, dilated arterial trunk, the aorta, arose from the central portion of the base of the heart and followed a normal course to the left. Behind this vessel was a large atrium with an appendage reaching forward on each side. The coronary vessels followed in general the usual distribution. The superior vena cava received a large vessel from below just before entering the atrial cavity through an orifice guarded by an Eustachian valve. The inferior vena cava was absent, the two hepatic veins entering the atrial cavity separately from below. The two pulmonary veins separately entered the right side of the atrial cavity.

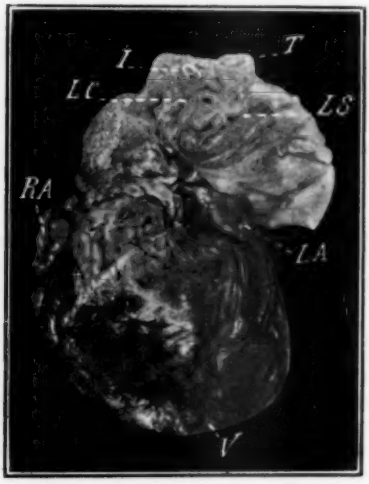

FIG. 1.—Case I, anterior surface of heart. *LA*, left atrial appendage; *RA*, right atrial appendage; *V*, ventricle; *I*, innominate artery; *LC*, left common carotid artery; *LS*, left subclavian artery; *T*, trachea.

On opening the atrium, a single large cavity with right and left appendages was disclosed (Fig. 3). There was no division into two chambers but the septum primum was represented as a broad flat band on the posterior wall of the atrium. A longer and thicker ridge on the anterior wall was the septum secundum. The persisting Eustachian valve was attached to the posterior wall of the atrium by a fenestrated membrane.

The atrial cavity communicated with that of the ventricle through a large orifice guarded by a single valve of five distinct cusps, for each of which there was a papillary muscle. The columnæ carniæ were well developed and produced deep intramural pockets as in the amphibian. The only attempt at interventricular septum formation was a thickened ridge on the left portion of the anterior ventricular wall. A small intramural thrombus was present at the apex of the heart where the wall was very thin. The aorta arose from the right side of the common ventricle and its valve was

composed of three well-developed cusps. The arch of the aorta was considerably dilated as far as the origin of the ductus arteriosus, but the arrangement of the great arterial trunks was normal. At the extreme

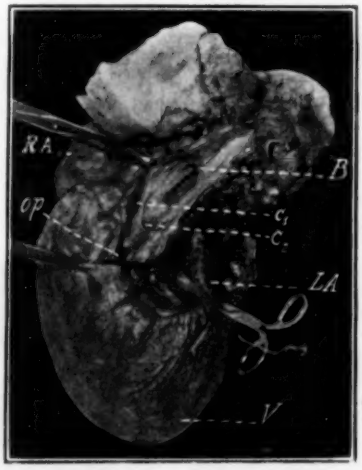

FIG. 2.—Case I, showing anomalies of pulmonary orifice. *op*, stenosed pulmonary orifice; C_1, C_2, pulmonary valve cusps; *B*, bifurcation of pulmonary artery; *LA*, *RA*, left and right atrial appendages; *V*, ventricle.

upper left corner of the ventricle the small stenosed pulmonary artery arose. (Fig. 2). Its orifice, 2.5 mm. in circumference, was guarded by a valve composed of a very small posterior and larger anterior cusp. The pul-

FIG. 3.—Case I, interior of atrial cavity. *svc*, superior vena caval opening; *hv*, orifices of the hepatic veins; S_1, S_2, septum primum and secundum; *O*, atrioventricular orifice; *pv*, pulmonary veins.

monary artery bifurcated 3 cm. from its orifice, the right branch receiving the patent ductus arteriosus whose diameter was over twice that of the pulmonary orifice.

The skull was opened and an extensive purulent basal meningitis was found. There was a marked pressure cone around the medulla and considerable flattening of the convolutions of the cortex. A culture of the pus revealed diplococcus meningitidis.

Other anomalies found consisted of an accessory spleen, markedly lobated kidneys and an undescended left ovary.

CASE II.—Baby M. was born on the obstetrical service, April 15, 1925. The mother was a healthy young mulatto primipara whose family history was not unusual. The paternal history could not be obtained. Labor was easy and no abnormality was noted at birth, the child weighing over 7 pounds and crying quite vigorously. A physical examination at the time revealed nothing of importance, and it was noted that the heart rate was 120 per minute and the pulse regular.

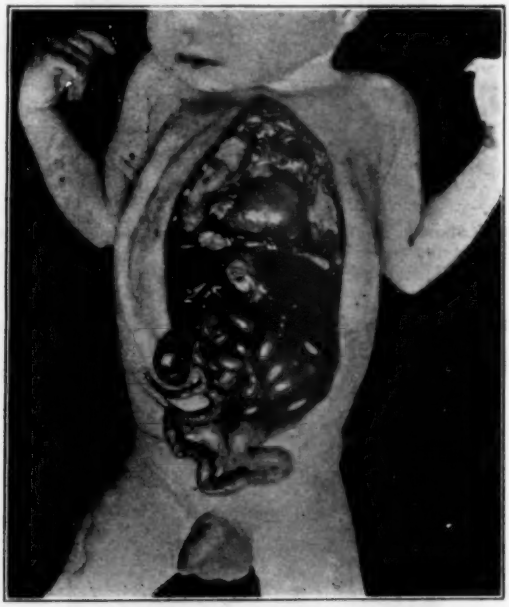

FIG. 4.—Case II, showing transposition of viscera.

The clinical course was not unusual for the first forty-eight hours, the child nursing well and the temperature and pulse remaining normal. Fifty-six hours after birth the temperature fell to 97° F. and the pulse rose to 150 per minute. At sixty hours, the baby refused to nurse. Four hours later cyanosis was quite marked, respiration very rapid and the pulse from 180 to 200 beats per minute. Moist râles were heard throughout both lungs and, although the extreme tachycardia made auscultation very difficult, a continuous murmur was heard over the entire precordium. At this time an impression of congenital heart disease, probably pulmonary stenosis, was recorded. The signs of cardiac failure rapidly increased and death occurred seventy-two hours after birth.

NECROPSY. The pleural cavities contained a moderate amount of straw-colored fluid, and the lungs, which were crepitant throughout, each presented three atypical lobes.

Immediately upon opening the peritoneal cavity it was seen that there existed a complete transposition of viscera, a minute description of which is not within the scope of this article (Figs. 4 and 12).

FIG. 5.—Case II, anterior surface of heart. *A*, atrium; *a*, truncus arteriosus; *V*, ventricle.

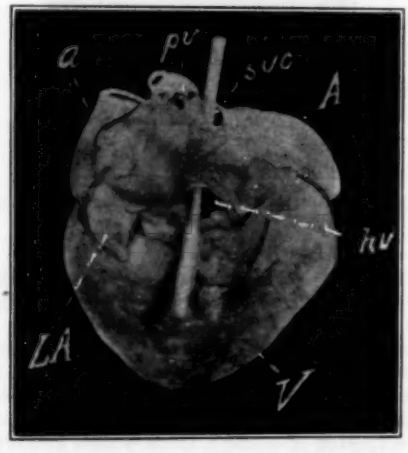

FIG. 6.—Case II, posterior surface of heart. *A*, atrium; *V*, ventricle; *a*, truncus arteriosus; *LA*, left atrial appendage, *svc*, superior vena cava; *pv*, pulmonary veins; *hv*, hepatic veins.

The pericardium was normal but the unusual appearance of the heart was at once apparent (Fig. 5). Its shape was roughly that of an equilateral triangle lying largely to the right of the midsternal line. From the left upper corner arose a large vessel, the truncus arteriosus, which arched to

the right to descend behind the heart. On the right upper corner was seen the right appendage of the atrium, which was distended with blood.

Posteriorly the same general configuration was observed (Fig. 6). A small, rudimentary left atrial appendage lay immediately behind the truncus arteriosus. The superior vena cava entered the atrial cavity from above. The inferior vena cava was lacking, and the two hepatic veins separately pierced the fibrous pericardium to enter the atrium from below. The two pulmonary veins entered the left atrium separately but no trace of a pulmonary artery was seen to leave the heart. The course of the coronary vessels was somewhat irregular but they followed in general the usual plan of distribution.

On first inspection, there seemed to be but a single atrium which communicated with the common ventricle through a large atrioventricular orifice (Fig. 7). The atrioventricular valve was composed of a large anterior and a smaller posterior cusp, each having a large papillary muscle.

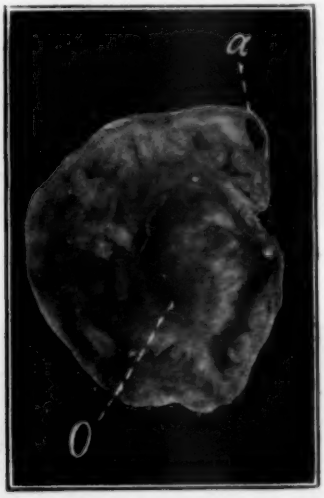

FIG. 7.—Case II, interior of atrial cavity. *a*, truncus arteriosus; *O*, atrioventricular orifice.

The right atrial appendage was large and distended with blood, communicating with the rudimentary left atrium through a large defect. This foramen was due to the lack of fusion of the incompletely developed septum primum and secundum. After a careful exploration this small left atrium was found to communicate with the ventricle through a minute, devious channel which would admit only a probe of medium-sized silkworm gut. No vestige of valve formation could be found along this channel (Fig. 10).

The ventricle consisted of a single thick-walled chamber without vestige of septum formation. There were large anterior and posterior papillary muscles, one for each of the atrioventricular cusps. A flexible probe passed through the small left atrioventricular canal, entered the posterior aspect of the ventricle near the origin of and behind the posterior papillary muscle.

The great vessels were very primitive in type. The truncus arteriosus arched to the right and descended along the right of the spine. From the arch sprung two innominate stems, the left giving rise to the pulmonary artery about 1 cm. from its origin. The latter vessel soon bifurcated to send

a branch to each lung. The two innominates passed upward, each dividing into a carotid and subclavian artery, but there was another unexplained anomaly in the form of a communication between the two innominate stems at the level of the third tracheal ring. The branches of the descending aorta were a mirror image of the normal (Fig. 8).

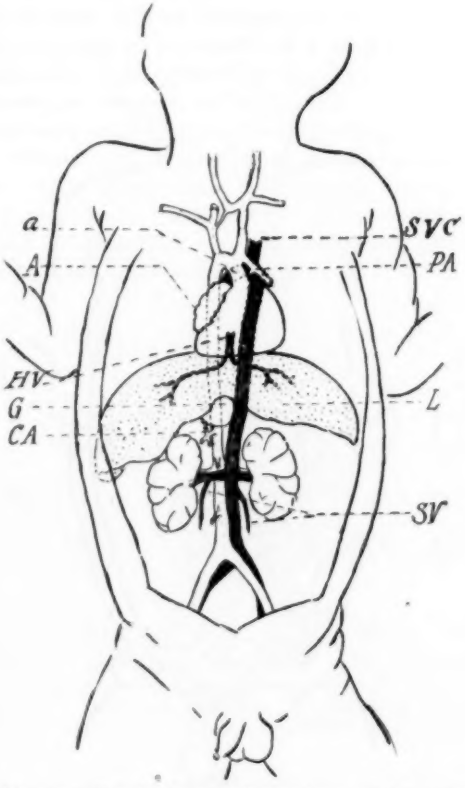

FIG. 8.—Case II, anomalies of the vascular system. *a*, truncus arteriosus; *PA*, pulmonary artery; *A*, atrium; *SVC*, superior vena cava; *HV*, hepatic veins; *G* gall bladder; *L*, liver; *CA*, celiac axis; *SV*, spermatic veins.

An unusual arrangement of the venous system was present. The vena cava was absent, the systemic veins draining into the azygos major which pierced the diaphragm and coursed upward on the left to enter the superior vena cava previously described. The portal system was a reversal of the normal, and the two hepatic veins entered the atrium separately from below. The complete transposition of viscera included even the spermatic veins, the left entering the azygos and the right the right renal vein (Fig. 8).

Symptomatology. For centuries congenital heart disease has been known as the "blue disease," or *morbus cæruleus*, though cyanosis may be conspicuously absent even in cases of marked defects, as is illustrated by the above cases, neither of which became cyanotic

until just before death. Another rather constant finding is an unusual coolness of the skin, as in Farre's[2] case of transposition of the aorta and pulmonary artery, which, on developing smallpox, had a slight elevation of temperature about the head but the trunk and extremities remained cool.

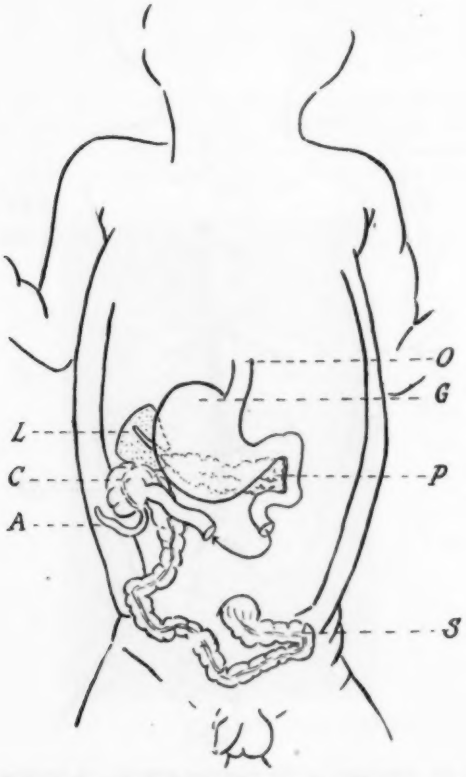

FIG. 9.—Case II, anomalies of alimentary canal. The unusual position of the cecum is probably due to an arrest in sinistro-rotation of the colon. *O*, esophagus; *G*, stomach; *L*, spleen; *C*, cecum; *P*, pancreas; *A*, appendix; *S*, sigmoid colon.

Clubbed fingers, dyspnea and cough are early and well-known occurrences. As in one of the above cases, the infant may have great difficulty in taking the breast. There may occur attacks of coma with convulsions, these usually being precipitated by excitement or physical exertion. A polycythemia is the rule, but one author[3] states that an anemia may occur in long-standing cases. Physical and mental development is often retarded.

General Consideration. The cases reported herein are examples of the most primitive human hearts that have been encountered (Fig. 10). Both were functionally two-chambered, and, according to

the usual practice of medical authors, could be reported under the title of "cor biloculare." However, they are both incompletely developed four-chambered hearts. Keith,[4] in a series of 272 cases, did not find an example of two-chambered heart. As he observes, the term "cor biloculare" is objectionable from an anatomic standpoint because in every animal having a pulmonary circulation there must be some attempt at formation of a double heart. The term is further confusing and misleading in that minor septal defects of varying degree are reported under this title. One such case[5] had a complete interatrial septum except for a small defect admitting only the tip of the little finger. It should be understood that such descriptive terms as "amphibian heart," "bilocular heart," and "single heart" refer to function rather than to structure, for anomalies are due to arrested development and the anlagen of the type characteristic of the species is always present.

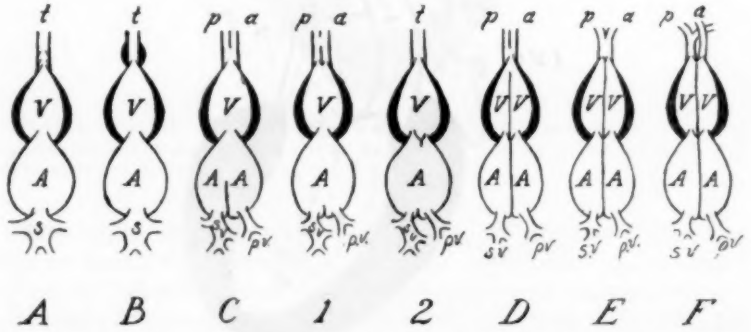

FIG. 10.—Diagram of comparative anatomy of vertebrate hearts. *A*, elasmobranchs; *B*, teleosts; *C*, amphibia; 1 and 2, cases described in this article; *D*, lower reptiles; *E*, alligator; *F*, birds and mammals. *A*, atrium, *a*, aorta; *p*, pulmonary artery; *pv*, pulmonary veins; *s*, sinus venosus; *sv*, systemic veins; *t*, truncus arteriosus; *V*, ventricle.

In general, developmental defects of the heart may be divided into four chief classes: (1) Abnormalities of the great vessels; (2) absence or arrested expansion of the infundibulum; (3) defects of the various septa; (4) deformities of the valves. Examples of all four classes are to be seen in the hearts herein described. In Case I there was a deformity of the pulmonary orifice and the outstanding lesion of gross defects of all the septa. In the second case may be seen the transposition of the great vessels, absence of expansion of the infundibulum and marked septal defects as well. These are all further complicated by a complete transposition of viscera.

Keith[4] found the persistence of the Eustachian valve, as in Case I, in but a single instance, and considers it the rarest of all cardiac malformations. Incomplete dissection probably accounts for the paucity of instances of venous anomalies presented in the above

cases. One similar case has been described recently by Miller.[6] Instances in which the pulmonary valve was composed of only two cusps are also rare. The unusual development of the columnæ carniæ is interesting in that it throws light upon the probable circulation in the cases reported above.

The circulation in the amphibian, as typified by the frog, is one in which there is a mixture of the aërated and nonaërated bloods. This admixture occurs first in the atrium and again in the ventricle whence it passes into the general circulation from which a part is diverted to the lungs. There is, however, a mechanism which tends

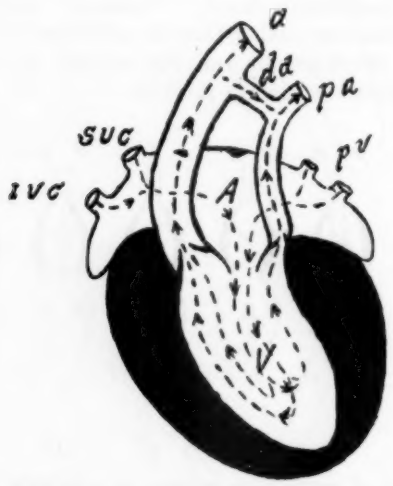

FIG. 11.—Case I, probable circulation. *a*, aorta; *da*, ductus arteriosus; *pa*, pulmonary artery; *svc*, superior vena cava; *pv* pulmonary veins; *ivc*, inferior vena cava; *A*, atrium; *V*, ventricle.

to keep separated the aërated from the nonaërated blood. At the beginning of diastole, because of the higher pressure in the pulmonary veins, the first volume of blood to enter the ventricle comes from these vessels and is stored within the pockets between the columnæ carniæ. The nonaërated blood then fills the remainder of the cavity. When systole begins, this upper layer of nonaërated blood is forced out first and, seeking the path of least resistance, enters the pulmonary circulation, where the pressure is lowest. As these vessels become distended the pulmonary pressure approaches that of the aorta and the last efforts of the systole forces the aërated blood from the intramural recesses into the general circulation.

This mechanism, we believe, existed in both of our cases. There is a minor difference between the two. In Case I the nonaërated blood entered the pulmonary circulation through both the pulmonary

orifice and the ductus arteriosus, while in the other case the abnormal pulmonary artery alone functioned (Figs. 11 and 12).

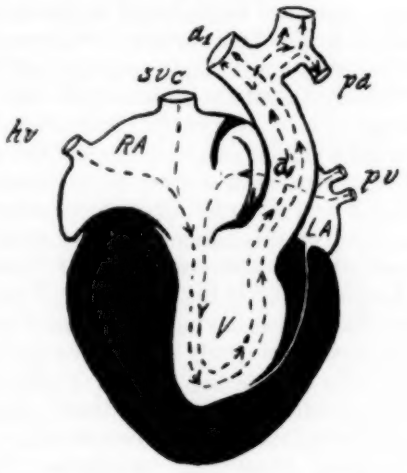

FIG. 12.—Case II, probable circulation. *a*, truncus arteriosus; a_1, aorta; *pa*, pulmonary artery; *svc*, superior vena cava; *hv*, hepatic veins; *pv*, pulmonary veins, *RA*, right atrium; *LA*, left atrium; *V*, ventricle.

Literature. We were able to find only 25 cases of "bilocular" human hearts reported in the literature. McDonald[7] has described a case of "bilocular" heart occurring in a girl aged sixteen years (?). In *another* discussion of the same case,[8] it was given as that of a girl aged twelve years, who was dyspneic and cyanotic from birth and who suffered from pulmonary tuberculosis. If the correct age of this patient was sixteen years, this ranks as the oldest reported case of such a cardiac defect. The description of the heart is somewhat meager, however, and the interior of the chambers is not described. The specimen cited by Gould and Pyle,[1] belonging to a youth of thirteen years, has already been mentioned. Valette,[5] in 1845, reported a case in a patient who lived to the age of six years, but the interatrial septum in this specimen was complete except for a defect which admitted the tip of the little finger. It is apparent that this was not a bilocular heart even in a functional sense. A few cases living from one to three years have been described, but the majority succumb within a few hours or a few days after birth.

In the cases reported under the term "cor biloculare" in the literature at our disposal, we have been unable to find any instance of a typical single heart. In all that were adequately described there was some vestige of an interatrial or interventricular septum. In many cases the septa were well developed except for small defects;[5] in others the description was too meager to justify an opinion, but

we cannot assume that they were very different from those fully described.

Apparently cases of cor triloculare, a primitive double heart, do occur. Numerous cases are to be found in literature, a review of which is beyond the scope of this article. Structurally, these cases usually present two atria and a single ventricle but the reverse may occur. Ewald[9] reported a patient with cor triloculare biventriculare who lived to the age of forty-two years. Hansemann in a discussion of this case reported a similar one who reached the age of sixty-two years. Fussell[10] reported such a case in an infant who was not cyanotic at birth but died of cardiac decompensation following pneumonia. The necropsy on this patient was performed by Dr. George Dock. One hundred and sixty-two cases of "morbus cæruleus" are listed by J. Lewis Smith[11] in his textbook. Twelve cases among that number were classified as having but a single atrium and a single ventricle! The source of this study is not given and we must assume that it is in error. He records only 4 cases of trilocular heart in his list, making the two-chambered heart three times as common. Nanagas[12] has described 2 cases of monoventricular three-chambered hearts having typical amphibian circulation. Other cases of so-called cor biloculare have been reported by Bernard,[13] Crisp,[14] Dalton,[15] Forster,[16] Guibert,[17] Moore,[18] Northrup,[19] Ramsbotham[20] and Abbott.[21]

Summary. Two cases of functionally bilocular human hearts are described. In one of the patients, a girl who lived to the age of fifteen years, the heart consisted of one atrium and one ventricle, in each of which there was evidence of septum formation which was arrested at an early stage of development. There was also stenosis of the pulmonary orifice, whose valve was composed of only two cusps, a patent ductus arteriosus, and anomalies of the great vessels. A very rare malformation, persistance of the Eustachian valve, was also present. The heart of the other case, functionally two-chambered, consisted of a single ventricle and a large right atrium, which was only partially separated from the rudimentary left atrium. The circulatory system was distinctly amphibian, a common truncus arteriosus giving rise to the pulmonary artery. The great vessels were very primitive in type and all anomalies were further complicated by a complete inversion of viscera.

The symptoms of congenital heart disease are very definite and striking, but there seems to be no analogy between their severity and the degree and extent of the cardiac defect. A review of the literature reveals that there is much confusion as to classification of congenital heart defects, and that such terms as "single heart" and "cor biloculare" are misnomers, for every animal with a separate pulmonary circulation must have present in some degree the anlagen of a double heart.

BIBLIOGRAPHY.

1. Gould and Pyle: Anomalies and Curiosities of Medicine, London, 1897, p. 296.
2. Farre, J. R.: Path. Res., Essay I, London, 1814.
3. Muhr, Lambert: Wurzb., 1889, **80**, 33.
4. Keith, A.: Lancet, 1904, i, 536; Lancet, 1909, ii, 359, 433, 519; J. Anat. and Physiol., 1912, **41**, 190.
5. Valette, A.: Gaz. méd. de Paris, 1845, 2s, **13**, 97.
6. Miller, A. James: Am. J. Pathol., 1925, **1**, 467.
7. Holt, L. E.: Arch. Pediat., 1895, **12**, 839.
8. Symington: Proc. Anat. Soc. Great Britain and Ireland, 1900, **34**, 15.
9. Ewald: Berlin klin. Wchnschr., 1889, **35**, 1044.
10. Fussell, M. H.: Med. News of Philadelphia, 1888, **3**, 496.
11. Smith, J. Lewis: Diseases of Children, 1896, 8th ed.
12. Nanagas, J. C.: Anat. Rec., 1921, **20**, 255.
13. Bernard, C.: Union Med. Par., 1860, 2s, **5**, 612.
14. Crisp: Trans. Path. Soc. London, 1846–1848, **1**, 49.
15. Dalton: Am. Med. Month., 1855, **3**, 224.
16. Forster: Trans. Path. Soc. London., 1846–1848, **1**, 48.
17. Guibert: Bull. Soc. anat. de Paris, 1860, **35**, 555.
18. Moore, C. U.: Heart, London, 1920–1921, **8**, 193.
19. Northrup, Wm. P.: Proc. New York Path. Soc., 1888–1889, p. 40.
20. Ramsbotham: Trans. Path. Soc. London, 1872, **23**, 80.
21. Abbott, Maude: Osler, Mod. Med., 2 ed. vol. **2**.

ELECTROCARDIOGRAPHIC CHANGES DURING ATTACKS OF ANGINA PECTORIS.

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The rarity of electrocardiographic observations in patients during attacks of angina pectoris makes this report seem desirable. Angina pectoris, here, is used to imply the paroxysmal attacks of pectoral pain which patients suffer who have coronary sclerosis, hypertension, or aortic insufficiency in contradistinction to the intractable attacks of pain due to occlusion of a coronary artery. The recurrence of the pain with effort and its relief through the exhibition of nitroglycerin is sufficient evidence to distinguish this pain from that seen in the occlusion patients.

Bousfield[1] reported a case observed during an attack of angina pectoris. The patient, who had aortic insufficiency, was subject to anginal attacks and by chance had a paroxysm while an electrocardiogram was being taken. The record during the attack was that of a right bundle-branch block (rate 95) and the record taken after the attack had completely subsided showed no defect in conduction, but did show inversion of *T* in Leads II and III (rate

88). Cowan and Ritchie state[2] that there may be electrocardiographic evidence of myocardial weakness during the attacks, viz.: flattening of *T* or *T* becoming negative, prolongation of the *Q-R* interval, and alteration of ventricular preponderance. With cessation of the attacks the electrocardiogram may return to normal.

Case Reports.—Case I.—J. M., a retired engineer, aged sixty years, widower, with two normal children was first seen on October 30, 1926, because of pain in the lower sternal region. This pain radiated laterally and was always occasioned by excitement or by effort—such as walking briskly. This pain occurred during the past twenty-two years—at first after strenuous effort and at long intervals. During the past few years the pain has increased in frequency and less effort has occasioned its production. His personal history included scarlet fever, pneumonia, and diphtheria as a child; gonorrhea in youth and syphilis at thirty-five years of age. For the latter, he received some treatment with arsphenamin and mercury. He has been a heavy smoker since the age of twenty (8 cigars and numerous pipefuls a day). He has not suffered dyspnea on effort, the pain pulling him up. The attacks of pain, always brought on by excitement or by effort, are especially severe after a heavy meal. They occur ten or fifteen times daily. There have never been attacks severe enough to require morphin. Recently he learned that nitroglycerin relieved his pains rapidly.

TABLE (J. M.).

	P–R*	R*	Q–R–S*	Heart rate.	Blood-pressure.
Before attack (Oct. 28, 1926)	0.138	0.055	0.071	88	
During attack	0.140	0.054	0.069	114–121	160/90
Immediately after attack .	0.141	0.056	0.063	111	
Five minutes after attack .	0.153	0.058	0.070	96	138/90
During attack (Jan. 25, 1927)	0.155	0.060	0.078	101	170/100
After attack	0.152	0.061	0.075	93	160/96

* Average interval in seconds.

Physical Examination. This revealed that the patient was a well-developed and well-nourished man who did not appear older than his age (sixty). He was in no discomfort. There was no cyanosis or dyspnea and no evidence of infection. The peripheral arteries were not sclerosed or tortuous. The heart rate was 104, regular and rhythmic. Blood pressure was 150 systolic; 80 diastolic. There was no cardiac enlargement—confirmed by orthodiagram. The aortic dullness was not increased. Over the aortic area was a systolic murmur, also heard over the entire precordium. No diastolic murmur was heard and the second aortic sound was not accentuated or tympanitic. The Wassermann reaction on the blood was negative. The urine and blood revealed no abnormality. An electrocardiogram was taken which showed normal mechanism, left preponderance, and inversion of *T* 3. The rate at this time was 88. While the electrodes were fastened to the patient, he complained of substernal pain and while nitroglycerin was being procured a record of Lead II was taken. This showed normal mechanism and inversion of the usually isoelectric portion of the curve between *S* and *T*. The end of *T* was upright (Fig. 1, *A* and *B*). The rate was 114. The patient was given one tablet of nitroglycerin (gr. $\frac{1}{100}$) by mouth and the pain rapidly subsided. Another electrocardiogram taken as the pain subsided showed less inversion of *T* (Fig. 1, *C*.). Five minutes later, the pain entirely gone, another record was taken, which revealed the

FIG. 1.—Electrocardiogram of J. M. (Lead II) taken (*A*) (*B*) during severe paroxysm of pain; (*C*) as pain was subsiding (October 30, 1926).

FIG. 2.—Electrocardiogram of J. M. (Leads I, II, III) taken after pain had subsided (five minutes after Fig. 1). (October 30, 1926.)

FIG. 3.—(*A*) Electrocardiogram of J. M. (Leads I, II, III) taken during a mild paroxysm of pain. (January 25, 1927.) (*B*) Electrocardiogram of J. M. (Leads I, II, III) taken after pain had entirely subsided. (Five minutes after Fig. 3.) (January 25, 1927.)

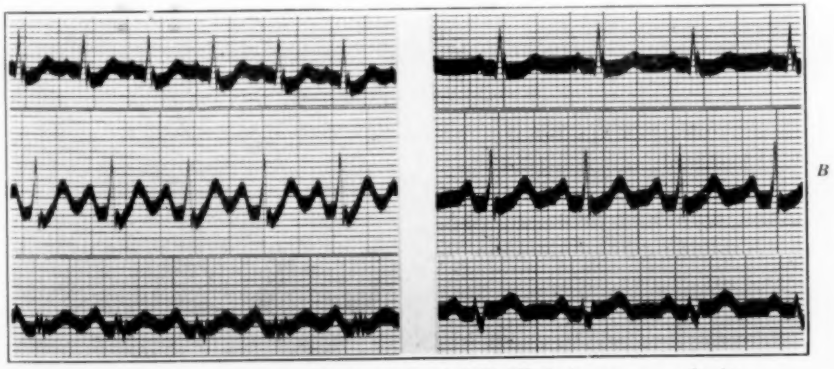

FIG. 4.—Electrocardiogram of M. R. (*A*) Leads I, II, III, during paroxysm of pain. (*B*) Leads I, II, III, without pain.

A *B* *C*

FIG. 5.—Electrocardiogram of H. T. (Leads I, II, III) taken (*A*) before attack; (*B*) during paroxysm of pain; (*C*) after pain had subsided.

S–T portion of the curve similar to that before the attack. (Fig. 2.) During the paroxysm the blood pressure was systolic, 160; diastolic, 90 and after the pain had subsided the blood pressure was systolic, 138; diastolic, 90.

A second series of observations was made on January 25, 1927. The patient climbed a flight of stairs and on coming into the laboratory complained of substernal pain. The physical examination revealed no change except that his blood pressure was systolic, 170; diastolic, 100. A few minutes later the pressure was systolic, 150; diastolic, 100—the pain having subsided. A record taken during the pain (Fig. 3, *A*), showed normal mechanism, left preponderance, and inversion of the portion of the curve between *S* and *T*, the end of *T* was upright. (Leads I and II.) This record was similar to that taken on October 30, 1926 during a paroxysm of pain. With subsidence of the pain the record (Fig. 3, *B*) was identical with that taken on the previous date under similar conditions. The blood pressure was then systolic, 150; diastolic, 90.

Some of the possible influences that might have operated in altering the *S–T* wave were investigated. *Vagus Stimulation.* Changes in vagal tone were first studied because of the possible reflex effects of its stimulation. The carotid sheath was firmly compressed by digital pressure. On right vagal stimulation the heart was profoundly slowed, the interventricular interval increasing from 0.76 second to 1.7 second. There was no change in the *P–R*, or *Q–R–S* intervals or in the direction or contour of *T* in Leads I and II. In Lead III the inversion of *T* increased from 3 mm. to 5 mm. There was no change in the *S–T* portion of the curve. On left vagal pressure the slowing of the heart was less (the interventricular interval increasing from 0.7 second to 0.8 second) and no change in the *S–T* complex was observed.

The Effect of Cold Water was Studied. It has been observed that the swallowing of cold water inverts the *T* wave.[2] Ice water was given to the patient. No change in the interventricular interval was noted and no change in the *S–T* complex or *T* wave was noted in any of the three leads.

Duration of Phases of Electrocardiogram. A study of the phases of the electrocardiographic heart cycle was made, employing the Lucas comparator. In the table these average measurements are recorded. The *P–R* interval did not change during the paroxysms of pain in either observation. Likewise right and left vagal pressure, respectively, and the drinking of cold water did not affect the duration of this interval. The duration of *R* and of the *Q–R–S* Group also were not affected. The interval between *S* and the beginning of *T* and between *S* and the point of maximum deviation of *T* did not suffer change.

Respiration. Respiration, while changing the heights of the initial ventricular complexes slightly (normal), caused no change in the *S–T* portion of the curve or of *T*.

Summarizing the electrocardiographic changes occurring in a patient on two separate occasions during anginal attacks the following observations were made: (1) The heart rate was slightly accelerated. (2) There was inversion of the *S–T* portion of the electrocardiogram in Leads II and III during the pain. (3) The electrocardiogram returned to its previous normal after subsidence of the pain. (4) At other times the *S–T* change could not be voluntarily produced.

CASE II.—(M. R.) *History:* A travelling salesman, aged thirty-six years, a married man with 1 child aged fifteen months, was first seen on June 25, 1927, because of pain across midsternal region brought on by excitement or effort. He had complained for two years. The pain radiated to the left shoulder and down the inner surface of the left arm. Hearty eating occasioned more pain. His personal history included appendicitis

in 1910, at which time an appendectomy was performed. He has never been a heavy smoker, but believes that he has some chest pains after smoking a cigar.

Physical Examination. A well-developed and well-nourished male, in appearance somewhat older than his years. The patient was comfortable when at rest. The accessible arteries were soft and the blood pressure was systolic, 194; diastolic, 120. The pulse was 120 per minute and was regular and rhythmic. There was no hyperesthesia of the chest. The heart was not demonstrably enlarged on percussion but the apex was rounded on fluoroscopic examination. There was a soft systolic murmur over the pulmonic area—otherwise the sounds were normal. The Wassermann test (blood) was negative. Electrocardiogram revealed left preponderance.

Observation During an Attack of Angina Pectoris. On July 9, 1927, the patient was again seen. His blood pressure was systolic, 170; diastolic, 110; and he had no pain while resting. His electrocardiogram was similar to that taken on the previous examination (rate 87). He sat up a number of times with resistance against his chest, a mild attack of angina resulting. This pain he described as if a "heavy load" were on his chest. The pain also radiated to the left shoulder. During the paroxysm the pulse rate rose to 133 and the blood pressure to systolic, 210; diastolic, 130. The *S–T* portion of the electrocardiogram (Fig. 4, *A*) in Leads I and II was somewhat depressed below the isoelectric level, *T* being upright and taller, while *R* became smaller (Lead II*) (Fig. 4, *A*). On subsidence of the paroxysm of pain the pulse rate fell to 106 and the *S–T* portion of the curve returned to its previous isoelectric position. (Fig. 4, *B*). The blood pressure fell to systolic, 190; diastolic, 118.

Duration of Phases of Electrocardiogram. The *P–R* and *Q–R–S* intervals were within normal limits before the attack and during the paroxysm of pain.

Case III.—(I. S.) *History.* A skilled laborer (aged fifty-two years, metal polisher) was first seen on July 9, 1927, complaining of substernal pain occurring with excitement and on physical exertion. These attacks occurred for about one year. There was no radiation of the pain. He was moderately dyspneic on effort. His past history included pleurisy and bronchitis fifteen years ago. He is married and has 4 children. He has never smoked nor drunk.

Physical examination showed the patient to be well-developed and well-nourished. There were a few crepitant râles in the right axilla, but the breath sounds were not altered. There was no demonstrable enlargement of the heart (confirmed by orthodiagram). The apex impulse was feeble and the first heart sound at the apex was faint. The peripheral arteries were soft and the brachial blood pressure was systolic, 130; diastolic, 80.

Observation During an Attack of Angina Pectoris. On July 11, 1927, an electrocardiogram was taken. This showed normal mechanism, with inversion of *P* 3 and *T* 3. The rate was 70. He was given a similar moderate exercise (sitting up a number of times against resistance), resulting in a paroxysm of moderately severe pain. The heart rate rose to 77. An electrocardiogram taken during the occurrence of the pain did not deviate from that recorded before the exercise.

Case IV.—(H. T.) *History.* A man, aged sixty-three years, married, with three children was seen on August 2, 1927, because of pain in substernal

* Changes noted by Smith in experimental ligation of the left coronary artery or its larger branches in dogs.

region (manubrium) coming on with the slightest effort. The paroxysms disappeared with rest or after taking nitroglycerin. The pain began fifteen years ago, first slight and only on severe exertion. Recently, however, slight exertion brought it on and the pain has been more severe. The pain has never radiated. He has cramplike pains in his calves on walking. His past history was unimportant. He has smoked approximately 10 cigarettes a day for years.

Physical Examination. The patient was a well-developed and well-nourished male in no distress while at rest. There was some evidence of arteriosclerosis, viz.: arcus senilis and tortuosity of the temporal arteries. The blood pressure was systolic, 180; diastolic, 90; pulse, 72, regular and rhythmic. There was slight cardiac enlargement, (chiefly of the left ventricle) confirmed by the orthodiagram. The first heart sound at the apex was slightly impure but was about normal in intensity. The aortic second sound was slightly tympanitic. Neither posterior tibial nor dorsalis pedis vessels were pulsating. His blood Wassermann was negative. Urinalysis revealed a faint trace of albumin and an occasional hyaline cast. The electrocardiogram showed normal voltage, mechanism normal with left preponderance.

It was concluded that the patient had sclerosis—arterial as well as arteriolar with symptoms referable to involvement of the coronary arteries and of the arteries of the lower legs. He was given nitroglycerin which relieved his pain.

Electrocardiographic Study. An electrocardiogram (Fig. 5, *A*) showed normal mechanism and no evidences of serious myocardial damage. He was given a mild exercise (raising his trunk against resistance). He complained of his usual substernal pain and an electrocardiogram taken immediately (Fig. 5, *B*) showed inversion of the *S–T* portion of the curve in Leads I and II and lowering of *T* in Lead III. No change occurred in the *P–R* or *Q–R–S* intervals. The heart rate before the attack was 67, during the attack it was 72, and after the pain subsided it was 79. The blood pressure during the attack was: systolic, 180; diastolic, 120; and systolic, 170; diastolic, 96, after the pain had entirely subsided. Fig. 5, *C* taken after the patient felt entirely free from discomfort showed a diminution in the inversion of *T* in Leads I and II, but there was some trace of the change seen during the attack.

Subsequent Course. The patient continued to use nitroglycerin for his pain with relief. Two weeks after the observations reported here he was seized with more severe substernal pain than he had previously suffered, he became cyanotic and acutely breathless. His pulse became almost impalpable, and there were numerous crepitant râles over the bases of his lungs. He died in twenty-four hours but there was no postmortem examination. The clinical impression was that of occlusion of a coronary artery or of a major branch.

Discussion. Changes have been noted in the *T* wave of the electrocardiogram following experimental ligation of branches of the coronary arteries[4] and following coronary occlusion in patients[5, 6, 7] In dogs, Smith showed that ligation of any branch of the left coronary arteries was immediately followed by increased prominence of *T* (varying directly with the size of the branch ligated), in twenty-four hours *T* became sharply negative (the larger the artery the greater the negativity). This change lasted three or four days after which it grew less until by the sixth or seventh day *T* again

was positive and *R* was low in voltage. After the fourth week, *T* again became isoelectric or negative. *T* sometimes became larger than *R*. Ligation of branches of the right coronary artery caused no consistent change in the electrocardiogram. The electrocardiogram of Case I shows inversion of *T* 1 and 2 and that of Case IV shows inversion of *T* 1 and 2 and flattening of *T* 3. These changes agree in some respects with the curves Smith recorded after experimental ligation. Case II shows some inversion of the *S–T* portion of the curve in Leads I and II, and *T* 2 became exaggerated. These findings again are similar to those of Smith. Case II showed no electrocardiographic change during a mild paroxysm of pain. This may have been due to the size of the vessels involved or to the fact that a branch of the right coronary was responsible for the symptoms.

Summary. Four patients suffering from attacks of angina pectoris presumably due to coronary sclerosis were observed electrocardiographically during paroxysms of pain. In three of these patients, there was inversion of the *S–T* portion of the curve in Leads I and II while the patients complained of substernal pain. The inversion was greatest in Lead II. The curves resumed their previous contours after the pain subsided. Further investigation was made on one patient whose electrocardiogram showed this change. Digital vagal stimulation, the drinking of cold water, and respiration failed to show any change in the electrocardiogram which was similar to that seen during the paroxysm. One patient showed no electrocardiographic change during the paroxysm of pain.

Conclusion. It is suggested from experiments (ligation of coronary arteries in dogs[4, 5, 8]) and clinical data (ligation of ramus descendens,[5]) and after recent coronary occlusion[7] that the changes observed in the *S–T* portion of the electrocardiogram of the patients now under study, represent transient vascular changes in the heart muscle.

BIBLIOGRAPHY.

1. Bousfield, Guy: Angina Pectoris: Variations in Electrocardiogram during Paroyxysm, Lancet, 1918, ii, 457.

2. Cowan, J. and Ritchie, W. T.: Diseases of the Heart, London, 1922, p. 392.

3. Wilson, F. N. and Finch, R.: The Effect of Drinking Iced Water upon the Form of the *T* Deflection of the Electrocardiogram, Heart, 1923, **10**, 275.

4. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Studies, Arch, Int. Med., 1918, **22**, 8.

5. Smith, F. M.: Electrocardiographic Changes following Occlusion of the Left Coronary Artery, Arch. Int. Med., 1923, **32**, 496.

6. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, Arch. Int. Med., 1920, **26**, 244.

7. Pardee, H. E. B., and Master, A. M.: Electrocardiograms and Heart Muscle Disease, Preliminary Report, J. Am. Med. Assn., 1923, **80**. 98.

8. Smith, F. M.: Further Observations on the *T* Wave of the Electrocardiogram of the Dog following the Ligation of the Coronary Arteries, Arch. Int. Med., 1920, **25**, 673.

THE THERAPEUTIC MECHANISM OF MALARIA TREATMENT OF GENERAL PARALYSIS: OBSERVATIONS ON A CASE.

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Ever since the inoculation of "artificial" malaria was introduced into the treatment of neurosyphilis, particularly general paralysis, and its definite therapeutic value recognized, speculation on the *modus operandi* has been rife. The present state of our knowledge forces us to draw a sharp dividing line as regards response to treatment between the manifestation of the early infections and some of those in the later stages. It must practically be conceded that arsphenamin usually acts as a true spirocheticide in the early infections, but later clinical symptoms resulting from syphilis may arise that do not show the expected response to treatment by arsphenamin or other drugs. This is particularly true in cases of general paralysis in which the standard drug therapy is so useless that doubt is at once cast on the diagnosis if the patient responds to treatment.

It is conceded by many that if a patient develops the malignant syndrome of general paralysis, some change in the biologic status differing decidedly from that seen in early neurosyphilis has taken place either in the invading *Treponema pallidum* or in the tissues invaded.

It was therefore not surprising, that with the actual establishment of the therapeutic value of artificial inoculation of malaria, one should hear of various hypotheses explaining the procedure, but it cannot be said that any one at present has preponderating evidence in its favor. The following case is reported because it suggests a factor in the therapeutic mechanism not emphasized in the hypotheses usually advanced:

Case Report. Case I.—A woman, aged thirty-five years, was seen at the Mayo Clinic for the first time in April, 1926. At this time, her memory, attention, and coöperation were exceedingly poor. A brief spell of apparent aphasia and stiffness of body had been noted in 1922.

Owing to the patient's mental condition, the physical examination was not satisfactory. It was noted, however, that the pupils were irregular, the reflexes exaggerated, and the speech halting. The Wassermann test on the blood was strongly positive on several occasions and the first spinal fluid examination showed the following: Wassermann test (Kolmer modification), 44444; Nonne, positive; small lymphocytes, 65; large lymphocytes, 4; polymorphonuclears, 14; colloidal benzoin, 023333333320000. These clinical and laboratory data seemed sufficient for a diagnosis of general paralysis.

April 16, a few days after admission, the patient was inoculated with malaria for therapeutic purposes. She passed through the usual course (Fig. 1), was dismissed from observation, and was seen again May 26. At this time (about six weeks after inoculation) there was definite slight

mental improvement but nothing of note with regard to the skin. She went home again with instructions to continue the use of quinin but was not given antisyphilitic treatment. September 26, she was seen again. The

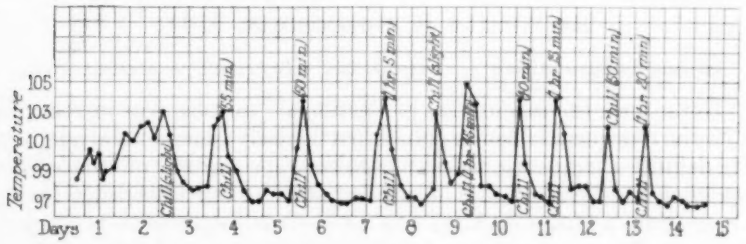

FIG. 1.—Temperature chart of patient during a course of malaria treatment.

improvement in her mental condition was striking. About five months after the inoculation the neurologist made the following note: "Truly a remarkable change, subjectively and objectively. She recalls her previous mental state, has regained her strength, her interest, her memory and her

FIG. 2.—The late syphilide on patient's buttocks.

mental activity." Despite this change in mentality, typical nodulo-ulcerative syphilides had developed on the inner side of the left thigh and right buttock (Fig. 2). She had noticed these lesions about two weeks

before her return in September. The eruption disappeared rapidly under arsphenamin injections and mercury inunctions. The spinal fluid was again examined September 29, and showed the following: Wassermann test (Kolmer modification), 4443—; Nonne, positive; small lymphocytes, 25; large lymphocytes, 4; colloidal benzoin, 033300333320000. The last examination of the spinal fluid April 21, 1927, showed: Wassermann test (Kolmer modification), 1—, Nonne positive; small lymphocytes, 4; colloidal benzoin, 001002332000000.

Comment. This case is particularly noteworthy because of the development of syphilide while the patient was recovering from the mental symptoms of general paralysis. For years, the fact has been accepted that a combination of late syphilide and neurosyphilis is rare; in fact, so rare that certain of the older syphilographers denied the coëxistence of these clinical manifestations of syphilis. Gennerich has particularly emphasized that such a combination means a benign course of the neurosyphilis and usually a satisfactory response to treatment. Bloch believes that the appearance of late syphilide is the external evidence of an allergic state or at least of the patient's partial immunity. This belief is well-founded and widely accepted. It need not necessarily follow that such immunity is strictly specific nor that the skin is necessarily the source of this immunity. The ability of the skin to develop a varying defense reaction has been conclusively demonstrated experimentally in tuberculosis. It is only necessary in this connection to call attention to Lewandowsky's painstaking investigations. That the tissue defense reaction is brought into play by the *Treponema pallidum* is suggested by the work of Brown and Pearce. Whether this defense reaction is a true cutaneous allergy and directly a phenomenon of the skin cells is a significant problem biologically. Bloch's ability to transfer the allergy seen in trichophytosis with a transplanted piece of skin from a sensitized to an unsensitized individual would allow of such a possibility provided the late syphilides are truly allergic in character. Such proof is, however, probably not necessary in order to concede to the skin at least some part in the defense reaction against syphilis.

At present we probably do not have a cutaneous test which would permit us to evaluate specific allergy in a given case of syphilis. Luetin has evidently not stood the test of critical study. Stokes has shown that luetin-like reactions can be produced by substances that do not contain the *Treponema pallidum* or its products. Sherrick found that iodides administered to normal persons would cause positive luetin reactions. Other investigations also discredited the specificity of the luetin reaction, and the test, therefore, will not aid in the estimation of the presence or absence of true allergy. It is possible that the entire defense reaction, including that of the skin, is nonspecific in syphilis.

With such considerations in mind, the observation of syphilide,

developing five months after inoculation with malaria, in a case in which late syphilide had never been manifested, lends support to the conception that malaria partially reëstablishes a lost immunity. That the neurologic symptoms caused by syphilis improved decidedly while the syphilitic lesions of the skin were developing is still further support of this belief and suggests the importance of the skin as one of the factors.

That we are dealing with an effect on the tissues rather than a direct effect on the *Treponema pallidum* is further suggested by the behavior of the spinal fluid in this case as well as in many others. Most observers agree that the serologic reactions of the blood and spinal fluid change only gradually. It is usually a matter of months and sometimes of a year or more before the spinal fluid becomes normal, even when the clinical response is fairly prompt and fully satisfactory. It will be noted that the spinal fluid showed slight improvement five months after the malaria treatment and decided improvement about a year later.

This patient had received treatment consisting of two injections of arsphenamin and forty inunctions of the Parke-Davis mercurette type after the lesion had appeared on the skin. Mental improvement had begun, however, before any such treatment was instituted. The amount of drug given could have had little effect on the serologic tests. Whether the results can be improved by some form of standard treatment later, and, if so, the time when such treatment should begin, are vital considerations in carrying out the malarial treatment. This case does not help to settle these problems and they need further prolonged critical study. The gradual improvement in the spinal fluid practically in all cases of general paralysis treated with malaria suggests an indirect mechanism rather than a direct spirocheticidal effect.

The correct evaluation of the effects of malaria treatment is of more than academic importance. As yet, its value in neurosyphilis, except in general paralysis, let alone other clinical manifestations of syphilis, is not proved. If the reëstablishment of a lost immunity could be demonstrated, malaria would offer a therapeutic approach to other forms of resistant syphilis that are now seemingly refractory to treatment.

Summary. Late syphilides are rarely seen in the presence of neurosyphilis. They are widely accepted as external evidence of an allergic condition of the body tissues and as such probably indicate at least a partial immunity. When they are present, a benign course of the neurosyphilis with ready response to treatment can usually be predicted. In this case a late syphilide appeared following a course of malaria. There was no evidence that the patient had ever had such a cutaneous lesion before. The syphilide appeared five months after the malaria treatment, and during this time the patient's mental and physical condition improved strikingly. This

course of events, then, suggested that the malaria treatment reëstablished a partial immunity in which the skin played a definite part. The gradual rather than rapid improvement of the spinal fluid in this case, as in so many others, further supports the conception that the mechanism of malaria treatment is, at least in part, explainable on the basis of a tissue reaction rather than of a direct spirocheticidal effect. Whether or not this conception, if correct, can be put to practical use in timing further standard treatment for neurosyphilis or other forms of resistant syphilis properly will have to be left to future critical study.

BIBLIOGRAPHY.

1. Bloch, B.: Stoffwechsel und Immunitätsprobleme in der Dermatologie, Cor.-Bl. f. schweiz. Aerzte, 1917, **47**, 993.
2. Bloch, B. and Massini, R.: Studien über Immunität und Ueberempfindlichkeit bei hyphomyzetenerkrankungen, Ztschr. f. Hyg. u. Infectionskrankh., 1909, **62**, 68.
3. Brown, W. H. and Pearce, Louise: Experimental Production of Clinical Types of Syphilis in the Rabbit, Arch. Derm. and Syph., 1921, **3**, 254.
4. Gennerich, Wilhelm: Die Syphilis des Zentralnervensystems, Berlin, J. Springer, 1922, pp. 255.
5. Lewandowsky, F.: Tuberkulose-Immunität und Tuberkulide, Arch. f. Derm. u. Syph., 1916, **123**, 1.
6. Sherrick, J. W.: The Effect of Potassium Iodid on the Luetin Reaction, J. Am. Med. Assn., 1915, **65**, 404.
7. Stokes, J. H.: A "Luetin" Reaction in Syphilis Produced by Agar, J. Am. Med. Assn., 1917, **68**, 1092.

EFFECT OF ONE HUNDRED INJECTIONS OF TRYPARSAMIDE UPON THE SPINAL FLUID IN GENERAL PARALYSIS.

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It may fairly be said that the question whether in patients with neurosyphilis the effort to render the spinal fluid negative should be in all circumstances unswervingly persisted in is a question which cannot be dogmatically answered on the basis of our present knowledge. In the first place, there are two different aspects to the problem. These are: (1) Must we render the spinal fluid negative in all cases of asymptomatic neurosyphilis—in patients who present no symptoms but in whom pathologic changes in the spinal fluid have been discovered? (2) In cases of clinical neurosyphilis, such as general paralysis and tabes, should we, after obtaining the maximum remission of symptoms possible in the given case, continue treatment unabated in the attempt to overcome the Wassermann reaction in the spinal fluid?

The first of these—the question as it presents itself *a fronte*—is somewhat analogous to the knotty problem as to whether the pres-

ence of a positive Wassermann reaction in the blood (latent syphilis) should be made the object of therapeutic attack. Many believe it should, even although it is known that in many patients—it would be well if we had some means of appreciating how many—the presence of a positive Wassermann reaction in the blood is entirely compatible with life-long freedom from symptoms. Similarly, do we actually know that all patients with strongly positive spinal fluids, especially when intractable to two or more courses of arsphenamin, will inevitably develop general paralysis or tabes? that all such patients are necessarily *paresis sine paresi*, pre-paresis or pre-tabes? I think we do not; yet, from the standpoint of practice, and in the presumed best interest of the patient, most of us would proceed as in asymptomatic or latent somatic syphilis, steering our course as though the potentiality, which we have no present means of estimating, were inevitably to become sooner or later the actuality.

The second question—the problem as it presents itself *a tergo*—has come into greater prominence, at least in the case of general paralysis, since the advent of treatment with malaria; for this therapeutic procedure has made it possible to return many patients with outspoken general paralysis to approximately their previous state of health, although at the same time an appreciable proportion of them continue for an indefinite period, it would seem, to harbor a more or less strongly positive Wassermann reaction in the spinal fluid.[1, 2] Again we do not know in cases of this sort whether the persisting Wassermann reaction is something of the nature of a residual scar, or whether it means that such patients, in contrast to those who ultimately become Wassermann-negative in the spinal fluid, are enjoying a clinical remission in the more purely literal sense of the word. The latter is perhaps the more reasonable, as it is obviously the safer, assumption to make; and I have felt justified in fact, in deriving from my personal experience the purely tentative belief that it may be only among the eventually negative patients that clinical remissions of extended duration will be found, while the persistence of a more or less strongly positive Wassermann reaction in the spinal fluid, even in cases representing initially an equal therapeutic success, may prove to be the harbinger of eventual relapse.[2] But it is to be hoped that the further passage of time will compel the abandonment of this mere suspicion.

From the purely scientific standpoint, then, a definite attitude of skepticism toward the problem remains justified. And it is a pleasure to find this point of view as cogently set forth as in the able phraseology of Stokes, whose words I would take the liberty of quoting in full:

"The third issue (the question of serologic interpretation) is perhaps the most important of all, for it raises the entire question of the direction and aim of treatment in neurosyphilis. Do we know at the present day whether it is, after all, for the ultimate best inter-

est of the patient to have his spinal fluid Wassermann rendered negative, his pleocytosis and globulins returned to normal? We do not know, we only infer that it is. We infer that these abnormalities are symptoms of the disease, to be removed as part of a restoration to normality if it can be accomplished without too great effort and cost. Neurologists particularly have very properly asked what normality is in neurosyphilis, and whether serologic normality is a necessary part of it. Is it justifiable to continue to "pummel" the asymptomatic patient mercilessly with treatment, or to treat another long after symptoms have become quiescent or disappeared? Is it necessary or desirable to keep him under physical, mental, and financial strain, and for merely "paper" findings, perhaps to predispose him to relapse as soon as the inhibitory effect of treatment is removed, or even before it is removed? There can be no doubt that able men are arrayed on both sides of this question, and that such observers as Nonne on the neurologic side and Wile on the syphilologic side must be listened to when they contend that serologic findings are not conclusive or even at times important elements in a decision to continue or to stop treatment. . . . The presence of Wassermann bodies, as we now well know, bears a somewhat qualified relation to the presence or absence of grave lesions of syphilis."[3]

Yet from the practical standpoint it perhaps continues for the present to be the part of conservatism, a species of insurance, to regard the disappearance of abnormal spinal fluid findings as a reasonable and legitimate aim when one is confronted with such findings either prior to the advent of clinical manifestations of neurosyphilis or subsequent to their therapeutic abolition or control. Since the malaria treatment—which I have come to believe is indicated in proved cases of pre-paresis and pre-tabes no less surely than in clinical general paralysis—is often but moderately successful, and usually only after many months, in bringing about definite modification in the spinal fluid Wassermann reaction, the question arises, for those who believe in the desirability of such modification, as to the amount of specific treatment necessary to produce it. Owing to the poor success in this direction which generally attends the use of arsphenamin, unless given in the form of arsphenamized serum, in neurosyphilis of the parenchymatous type, the choice of arsenical preparation will usually fall upon tryparsamide; and the question then becomes: how much of this agent will in all probability be required to bring about sterilization of the spinal fluid in these cases? Solomon and Viets,[4] indeed, have already stated that upward of 50 or 75 injections of tryparsamide (of 3 gm. each) are frequently needed for the purpose. From this standpoint, it has seemed worth while to state briefly our experience with a few patients to whom more than 100 injections of tryparsamide have been administered, including also, for the sake of comparison, certain others who have received a smaller amount of this drug.

TABLE I.—RESULTS OF LONG CONTINUED TREATMENT OF PARESIS WITH TRYPARSAMIDE.

Name.	Total number doses tryparsamide.*	Total period of treatment.	Spinal fluid findings subsequent to total period of treatment.				
			Wassermann reaction.†			Albumin,‡ (mg. per 100 cc.)	Colloidal gold.§
			1 cc.	0.5 cc.	0.2 cc.		
(a) More than 100 doses							
1. R. J. S.	116	3 9/12 yrs.	A. ++++ C. ++++	+++ ++++	+ ++	90	1123331100
2. J. M.	116	4 0/12 yrs.	A. ++++ C. ++++	O ++++	O ++++	50	5555433210
3. H. R.	108	3 1/12 yrs.	A. ++++ C. ++++	O ++++	O O	60	5555543210
4. W. H.	108	3 7/12 yrs.	A. O C. ++++	O ++++	O O	40	3333321100
5. J. B.	106	3 8/12 yrs.	A. O C. ++	O O	O O	40	4444421100
(b) 55 to 81 doses							
6. E. H.	81	3 11/12 yrs.	A. ++++ C. ++++	++++ ++++	++++ ++++	55	4432211000
7. C. A.	75	3 7/12 yrs.	A. ++++ C. ++++	++++ ++++	++++ ++++	70	4544432000
8. H. A. L.	70 (M)	3 8/12 yrs.	A. ++++ C. ++++	+++ ++++	O ++	45	3345321100
9. G. F.	65 (M)	1 9/12 yrs.	A. ++++ C. ++++	++++ ++++	O +	60	4555431100
10. E. L.	65	1 5/12 yrs.	A. ++++ C. ++++	O +	O O	30	
11. M. K.	64 (M)	1 7/12 yrs.	A. ± C. ++++	O +	O ±	60	5555432100

12. S. M.	63 (M)	1 11/12 yrs.	A. ++++	++++	+++	...	5554321000
			C. ++++	++++	++++		
13. J. P. S.	60	1 3/12 yrs.	A. +++	O	O	90	5555543210
			C. ++++	++++	+++		
14. S. A.	60	2 8/12 yrs.	A. ++++	+	O	125	
			C. ++++	+++	O		
15. J. S.	55 (M)	1 9/12 yrs.	A. ++++	+	O	85	4443321000
			C. ++++	++++	++		
(c) 48 *doses or less*							
16. J. G. R.	48 (M)	1 1/12 yrs.	A. ++++	O	O	65	5444432100
			C. ++++	++++	O		
17. W. J. L.	48 (M)	1 2/12 yrs.	A. O	O	O	40	
			C. O	O	O		
18. J. R.	40 (M)	2 6/12 yrs.	A. ++++	++++	++++	50	
			C. ++++	++++	++++		
19. F. S.	36 (M)	10/12 yrs.	A. ++++	+	O	50	3345321000
			C. ++++	++++	+++		
20. W. B.	36 (M)	10/12 yrs.	A. ++++	+++	O	50	5443322100
			C. ++++	++++	±		
21. M. F.	36 (M)	9/12 yrs.	A. ++++	++++	++	75	5555433210
			C. ++++	++++	++++		
22. J. H.	36 (M)	10/12 yrs.	A. ++++	++++	++++		
			C. ++++	++++	++++		
23. G. K.	24	6/12 yrs.	A. O	O	O	50	0000000000
			C. O	O	O		

* 3 gm. to the dose. In a few patients who received 2.5 gm. or 3.5 gm., the dosage is here adjusted to a 3-gm. basis.

† The Wassermann technique employed is that of the New York State Department of Health: sheep system, with four-hour ice-box fixation. The A. and C. in this column refer to the 2 antigens used: A = acetone insoluble; C = cholesterinized antigen.

‡ For the quantitative estimation of albumin we have employed the rapid clinical method recently suggested by Young and Bennett.[5]

§ These curves were obtained with a colloidal gold suspension titrated with permanent H-ion concentration standards, and having a pH of 7.0, in accordance with the technique employed by Christina and Green.[6]

Our results are summarized in Table I. The clinical material here presented consists of male patients with general paralysis of at least moderately advanced character, such as in every instance necessitated commitment to a hospital for the insane. In every case the Wassermann reaction in the spinal fluid was strongly positive (++++ with 0.2 cc.) prior to instituting treatment.

Twelve of these patients, designated (M), were given the malaria treatment three months to a year before tryparsamide was begun. Although in some instances fever therapy exerts a very definite influence upon the spinal fluid findings in the course of a considerable lapse of time (one to two years or longer[2]), so that in some of these patients the result reported may not have been due to tryparsamide alone, these cases are included here for the reason that in others it is obvious that the malaria treatment exercised no adjuvant influence whatever.

Four patients (Nos. 1, 3, 6, 10) received in addition to tryparsamide a course of 12 injections of neoarsphenamin of 0.6 gm. each, given between two courses of tryparsamide, and a fifth (No. 7) a course of 12 injections of sulpharsphenamin as well; 3 patients (Nos. 8, 12, 22) received both malaria and neoarsphenamin in addition to tryparsamide. But, as may be noted, there is little in the serological status of these patients to warrant the ascription of a favorable influence on the part of this additional arsenical treatment.

All the patients here shown are still living, with the exception of No. 14, who died within two months of his sixtieth injection of tryparsamide.

Only 2 patients of the series have been under observation for less than two years. Of the 5 patients under (*a*), 2 have attained an excellent clinical remission, now of nearly four years' standing; good remissions have occurred in 7 of the 10 patients listed under (*b*), although in only 2 of these (Nos. 6 and 7) is the remission ascribable to tryparsamide; a similar clinical outcome is observable in only one (No. 18) of the 8 cases listed under (*c*), a result again not directly ascribable to tryparsamide but to the malaria which preceded it.

The results shown in Table I are schematized, more or less roughly, in Table II.

TABLE II.—SUMMARIZED RESULTS.

Wassermann reaction.	Number of cases.	Doses of tryparsamide.
Unchanged	6	36 to 81
Slightly modified:		
Negative with 0.2 cc.	4	36 to 70
Modified:		
Negative with 0.5 cc. acetone-insol. antigen only	8	36 to 116
Much modified:		
Negative with 0.5 cc., both antigens	3	64 to 106
Negative	2	24 and 48
	23	

Thus we have, at one extreme, 6 patients in whom the Wassermann reaction in the spinal fluid has remained essentially unchanged—and while it is true that 3 of these have received only 36 to 40 injections of tryparsamide (plus malaria), the other 3 have had 63, 75, and 81 doses; and at the other extreme, 2 patients in whom the spinal fluid has become completely negative after only 48 (plus malaria) and 36 doses of tryparsamide, respectively. The remaining 15 patients occupy more or less intermediate positions, as a result of a total amount of tryparsamide ranging (with 3 exceptions) from 65 to 116 doses. These results are scarcely superior to those which the malaria treatment unaided is capable of producing, since in our experience the spinal-fluid-Wassermann reaction eventually becomes completely negative in about 20 per cent, and materially modified in an additional 20 per cent, of patients treated with malaria alone;[2] speaking very roughly, not less than 75 injections of tryparsamide would seem to be in general the equivalent, in sterilizing effect, of a course of fever therapy.

When it is considered that the 5 patients who have received more than 100 injections of tryparsamide compare fairly favorably on the whole with most of the others, and when in especial it is taken into account that these patients did not exhibit their present status until this number of injections had been given, but on the contrary remained immovably positive until at least 60 to 75 doses had been administered, it may be provisionally concluded that, despite the rather wide range of individual response observable, it will usually require not less than 100 injections of tryparsamide, and certainly not less than 60, to bring about any really material degree of modification of the Wassermann reaction in the spinal fluid. As regards complete negativity, however, full assurance is still beyond reach; nevertheless, the very gradual but at the same time steady improvement shown by even our most refractory cases after the 75- to 100-dose level had been passed holds out the promise that in no case perhaps, is this aim impossible of ultimate achievement, if—at the cost of upward of 150 injections of tryparsamide—this object should seem desirable of attainment.

Summary. 1. In the present state of our knowledge it is impossible either to affirm or to deny the necessity for a persistent attempt to render the spinal fluid negative in cases of probable parenchymatous neurosyphilis, either prior to the onset of symptoms or subsequent to their control or abolition. Where it seems desirable to pursue such an aim, tryparsamide is without doubt the arsenical drug of choice for the purpose.

2. In a series of 23 patients with general paralysis investigated from this standpoint, it was found that, whereas the reactivity of the spinal-fluid-Wassermann reaction was distinctly variable, consistent results were scarcely obtained with fewer than 80 injections of tryparsamide of 3 gm. each; thus, the 5 patients who have received

more than 100 injections, though their spinal fluids are even yet not negative, compare favorably on the whole with the others.

3. The definite influence which has eventually been exerted upon even the most immovably positive spinal fluids suggests that complete negativity may perhaps always be capable of achievement, although in general at the cost of well upward of 100, or even 150, injections of tryparsamide.

BIBLIOGRAPHY.

1. Ferraro, A. and Fong, T. C. C.: The Serology of General Paresis in the Malaria-treated Cases, New York Med. J., 1926, **134**, 562, 607, 682.

2. Bunker, H. A., Jr.: The Influence of the Malaria Treatment upon the Spinal Fluid Findings in General Paralysis, Arch. Neur. and Psychiat., (to be published).

3. Stokes, J. H.: Modern Clinical Syphilology, W. B. Saunders & Co., Philadelphia, 1926, 949.

4. Solomon, H. C. and Viets, H. R.: Tryparsamide Treatment of Neurosyphilis: Second report, J. Am. Med. Assn., 1925, **85**, 329.

5. Young, G. A. and Bennett, A. E.: Studies on the Quantitative Estimation of the Total Protein Content in Cerebrospinal Fluid, Am. J. Med. Sci., 1926, **172**, 249.

6. Christina V. and Green, C. S.: The Preparation of Gold Solutions and their Titration with Permanent H-ion Concentration Standards, J. Lab. and Clin. Med. (to be published).

REVIEWS.

A Treatise on Orthopedic Surgery. By Royal Whitman, M.D., M.R.C.S., F.A.C.S. Eighth edition. Pp. 1061; 954 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $9.00.

In the publication of the eighth edition of his Orthopedic Surgery, Whitman has done two things, first, he has selected what he considers proven and practical methods from the offerings of writers upon related subjects and second, he has recorded what time and most active and extensive experience have shown to his own judgment to be sound, reliable and practical. No man of the present day has greater, and few have had as great opportunity to demonstrate the value of various methods in different conditions of this specialty and while many of experience will take issue with some of his statements, none can deny his honesty of contention and originality of thought in his presentations.

This book is a comprehensive and most valuable publication and can be most heartily recommended as a guide and a standard of orthopedic conditions for the student and practitioner, because it is more a record than a compilation. J. R.

Manual of Chemistry. By W. Simon and Daniel Base. Thirteenth edition, enlarged and revised by John C. Krantz. Pp. 695; 55 illustrations. Philadelphia: Lea & Febiger, 1927.

This is an improved edition of an old manual which was written to be a general guide in chemistry for beginners in medicine, pharmacy and dentistry and which is probably intended also as a general reference book in elementary chemistry for physicians. Several sections dealing with modern topics have been added to the book (theory of solutions, etc.) but these are later additions whose method of treatment does not permeate the book as a whole. The general view point is not modern, but as an elementary reference work and compendium, it no doubt has a place in the medical library.

J. A.

FISTULA OF THE ANUS AND RECTUM. By CHARLES JOHN DRUECK, M.D., F.A.C.S. Pp. 318; 66 original illustrations. Philadelphia: F. A. Davis Company, 1927. Price, $3.50.

FOR years the reviewer has been confronted by statements from students that fistula in ano are tuberculous in origin. The results of the operative treatment have uniformly been so poor in the hands of the profession at large that a cause such as tuberculosis has been used as an excuse to salve conscience possibly. For the above reasons, if for no other, the present book is timely and well chosen. The writer is especially qualified to have his ideas and suggestions carried out because of his vast experience as a teacher in this branch. The anatomical, pathological, physiological and clinical knowledge offered here are the result of many years observation. It is only through the proper consideration of the above that the odious position of surgery of anal fistula can be bettered. As the author states, any one can stick a probe through the fistula somewhere into the bowel and lay the tract open, but a careful operation based on the above premises is the only true surgical procedure. The subject is extensively, thoroughly and carefully presented in a very clear, readable style. E. E.

CLINICAL DIAGNOSIS BY LABORATORY METHODS. By JAMES CAMPBELL TODD, PH.B., M.D., Professor of Clinical Pathology, University of Colorado School of Medicine and ARTHUR HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, University of Minnesota (Mayo Foundation). Sixth edition. Pp. 748; 346 illustrations. Philadelphia: W. B. Saunders Company, 1927.

SEVERAL years personal acquaintance with this book has convinced me that it is one of the most practical and accurate in its field for hospital laboratory use. The present enlarged edition includes several new tests in blood chemistry, liver function, syphilis, etc., and the chapter on Parasites is entirely rewritten. Dr. Sanford now appears as co-author. E. K.

THE THOMAS SPLINT AND ITS MODIFICATIONS IN THE TREATMENT OF FRACTURES. By MEURICE SINCLAIR, C.M.G., M.B., CH.B. (EDIN.). Pp. 165; 123 illustrations. New York: Oxford University Press, American Branch, 1927. Price, $4.50.

THE author of this treatise is admirably fitted to present the subject of fracture treatment, being qualified by his vast experience in the English army during the World War.

To the casual reader the book seems too complex by reason of the multiplicity of apparatus. But to the experienced man the complexity really is simplicity and the many tricks and appliances are just those little touches that may make or mar success in a given case. As is well known, the mortality in Great Britain from compound fractures of the femur in 1916 was 80 per cent. This was reduced coincident with the advent of the Thomas treatment until it reached 7.3 per cent in 1918, a wonderful achievement accomplished by the use of the appliances so admirably described by Meurice Sinclair in this great little book. The principles and appliances are shown to be applicable to the treatment of fractures of other long bones as well. E. E.

A Textbook of Psychiatry for Students and Practitioners. By D. K. Henderson, M.D., F.R.F.P.S., Physician-Superintendent, Glasgow Royal Mental Hospital, and R. D. Gillespie, M.D., D.M.P., Physician for Psychological Medicine, Guy's Hospital, London: Oxford University Press, American Branch, 1927. Price, $5.50.

This work is dedicated to a foremost psychiatrist, Professor Adolf Meyer, who for years has approached his subject from the view point of *reaction types*, which is the basis of the new classification here offered. The volume is comprehensive and lucid, with eighty-four case reports appropriately distributed throughout the text. Cotton's work—focal infections—we are told needs control, and with propriety it might have been said, some of it needs to be stopped. The role of the endocrines being uncertain, they are given rather scant consideration. This is the best psychiatry yet published in English, and its popularity is predicted. N. Y.

Paracelsus. Sämtliche Werke. Nach der 10 Bändigen Huserschen Gesamtausgabe (1589–1591) zum Erstenmal in Neuzeitliches Deutsch Übersetzt. By Dr. Bernhard Aschner. First Volume. Pp. 1012; 1 illustration. Jena: Gustav Fischer, 1926.

The perennial interest attaching to the romantic figure of Philippus Aureolus Theophrastus Bombastus von Hohenheim (Paracelsus) as well as his "modern" spirit of independence and conflict with long established authority make it highly appropriate that his works should be available in modern language. Even the fact that his descendent, Sudhoff, is in the midst of a many-volumed edition of his works from Barth's press does not detract from the value of

Aschner's contribution, as Sudhoff's work retains the difficulties of sixteenth century German, often in Swiss dialect, and in the four volumes thus far published is chiefly concerned with philosophy and magic.

In this volume are found a biography of Paracelsus (24 pages); a bibliography (4 pages); short essays on his writings and his medical, philosophic and magic teachings, and his chief medical works: Volumen Paramirum (with the 5 Entia); Opus Paramirum, Bucher Paragranum and der Paragraphen, Tartarus, die Pest, die Drei Ersten Grundstoffe (salt, sulphur and mercury), etc. The number and contents of future volumes is not disclosed. Let us hope they will include a complete list of Paracelsus editions, in addition to the fragmentary list here given. E. K.

COMPENDIUM OF REGIONAL DIAGNOSIS IN AFFECTIONS OF THE BRAIN AND SPINAL CORD. By ROBERT BING, Professor in the University of Basle. Third American edition. Pp. 204; 102 figures and diagrams, many in colors. St. Louis: C. V. Mosby Company, 1927. Price, $6.00.

THIS translation from the sixth German edition shows but little change in the text, however, notable revision has been found necessary in the diagrams. In this practical work no effort has been made to delve deeply into theories. The volume is of especial value in localizing pathological processes in the central nervous system. Since it is possible to deduce the location of a lesion from its irritative and paralytic symptoms, there is here given a scientific explanation of this difficult matter in a way that is unusually clear. The text finds abundant support in the many useful figures and diagrams. N. Y.

SURGICAL ANATOMY OF THE HUMAN BODY. By JOHN B. DEAVER, M.D., Sc.D., LL.D., F.A.C.S. Second edition, three volumes. Volume II, pp. 854; 195 illustrations. Volume III, pp. 763; 159 illustrations. Philadelphia: P. Blakiston's Son & Co., 1927.

THE second and third volumes of this second edition of Surgical Anatomy are deserving of as great a reception as was given the first. The character of the subject matter is such as to demand accuracy in every detail, which accuracy is easily checked up by comparison with standard works on anatomy. These volumes are well edited and the author's world-wide reputation is sufficient recommendation. The illustrations are especially fine and the volumes are prepared very attractively with excellent quality of paper and binding. E. E.

BOOKS RECEIVED.

*Atlas Thoracoscopicon.** By DR. FELIX COVA. Pp. 50, 50 illustrations. Milan: Sperling and Kupfer, 1927. Price, $9.00.

*Special Dental Pathology.** By JULIO ENDLEMAN, M.S., D.D.S., F.A.C.D. Second edition. Pp. 444, 371 illustrations. St Louis: C. V. Mosby Company, 1927. Price, $7.00.

*Diseases of the Skin.** By HENRY H. HAZEN, A.M., M.D. Third edition. Pp. 572, 248 illustrations. St. Louis: C. V. Mosby Company, 1927. Price, $10.00.

Index Catalogue of the Library of the Surgeon General's Office, United States Army. Third series, Volume VI. Pp. 1240. Washington: Government Printing Office, 1926.

*Lehrbuch und Atlas der Laparo- und Thorakoskopie.** By DR. ROGER KORBSCH. Pp. 73, 37 illustrations. Munich: J. F. Lehmann, 1927.

*Four Thousand Years of Pharmacy.** By CHARLES H. LA WALL, PH.M., PH.D. Pp. 665, 64 illustrations. Philadelphia: J. B. Lippincott Company, 1927. Price, $5.00.

*Nutrition and Diet in Health and Disease.** By JAMES S. MCLESTER, M.D. Pp. 783. Philadelphia: W. B. Saunders Company, 1927.

Medical Clinics of North America. Tulane University Number, November 1927, Volume XI, No. III. Pp. 210, 46 illustrations. Philadelphia: W. B. Saunders Company, 1927.

*Laboratory Manual of Organic Chemistry for Students of the Medical Sciences.** By HUGH C. MULDOON, D.SC. Pp. 118, 8 illustrations. Philadelphia: P. Blakiston's Son & Co., 1927.

*Modern Aspects of the Diagnosis, Classification and Treatment of Tuberculosis.** By J. ARTHUR MYERS. Pp. 268, 34 illustrations. Baltimore: Williams & Wilkins Company, 1927. Price, $5.50.

*Die Serodiagnose der Tuberkulose.** By DR. MAX PINNER. Pp. 88. Leipzig: Johann Ambrosius Barth, 1927.

*The Normal Diet.** By W. D. SANSUM, M.S., M.D. Second edition. Pp. 136. St. Louis: C. V Mosby Company, 1927. Price, $1.50.

*Tobacco and Physical Efficiency.** By PIERRE SCHRUMPF-PIERRON, M.D. Pp. 134. New York: Paul B. Hoeber, Inc., 1927. Price, $1.85.

Surgical Clinics of North America. Pacific Coast Number, Volume VII, No. 5. Pp. 266, 132 illustrations. Philadelphia: W. B. Saunders Company, 1927.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Acute Disturbance of Lung Function in Pneumonia.—Barach (*J. Am. Med. Assn.*, 1927, **89**, 1865) calls attention to the fact that in lobar pneumonia the symptoms are due: (1) To the local lesion; (2) to the toxemia; (3) to pulmonary insufficiency, or anoxemia. He shows that in normal individuals with 75 per cent oxygen saturation of their blood, many symptoms are produced which are analogous to those which arise in the course of pneumonia in patients who are extremely cyanotic. As a result of the decreased oxygen tension of the arterial blood, the patient has to combat not only the toxemia of the disease, but also anoxemia. Toxemia may be combatted by various methods, none of which are very satisfactory. The anoxemia may, however, be very materially done away with by the giving of oxygen to the patient, but with this proviso, that if the oxygen saturation of the blood is raised with inhalations of oxygen, it is absolutely necessary to maintain that oxygen level until the patient recovers from the pneumonia. He instances 5 cases in which there was acute oxygen want as a result of the sudden stoppage of the gas before the disease had cleared up. Oxygen should be supplied to the patient who is markedly cyanotic, as shown by a leaden-gray pallor, who has markedly shallow breathing, rapid pulse, delirium and irrationality. The exact estimation of the oxygen saturation of the blood, of course, is to be desired, as despite the clinical symptoms occasionally cyanosis may be present if there is not sufficient hemoglobin to transmit the bluish color. To these patients oxygen should be given in sufficient quantities. The most practical method is to give 2 liters a minute from a high-pressure tank through a nasal catheter. This method has certain faults, but for ordinary purposes is infinitely better than any other method which has been previously employed. An oxygen tent in which the air is cooled and dried can increase the oxygen to 40 or 50 per cent, whereas the

inspired air by the catheter method contains approximately 30 per cent. An oxygen chamber affords a very accurate and exact method of giving oxygen to patients, but it is too expensive for ordinary use and can only be provided for by large institutions.

Further Observations on the Specificity of the Green-producing Diplococcus in Measles.—One of the criticisms that was made to the green-producing diplococcus of Tunnicliff as being the causative agent in measles is that similar cocci have been found during convalescence when the disease, measles, is not contagious. In the present publication TUNNICLIFF (*J. Inf. Dis.*, 1927, **41**, 267) explains this apparent discrepancy between these organisms which are pathogenic and those which are nonpathogenic. By an ingenious method of testing the opsonic strength of serums, she shows that the organisms produced in the preëruptive stage of measles and the early eruptive stage are immunologically distinct from similar cocci isolated during convalescence. The green diplococcus when grown in normal and immune horse serum, dextrose broth, loses its specificity, but this may be regained by growing on blood agar for a few generations. Likewise, growing the coccus at a temperature as high as 40° or 41° C. also removes the specificity.

SURGERY

UNDER THE CHARGE OF

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Tuberculosis of Knee Joint in the Adult.—HENDERSON and FORTIN (*J. Bone and Joint Surg.*, 1927, **9**, 700) say that their study is based on the records of 211 patients for whom the knee joint had been resected for tuberculosis. There was no operative mortality. One hundred and seventy-one patients (88.3 per cent) secured firm bony union with good function. Union failed in 22 cases (11.3 per cent). In 4 of these the bones were induced to unite by a bone graft, thus leaving 18 (9.2 per cent) in which union did not occur. The use of the bone graft as a routine and the improved technique of operation should give a lower percentage of nonunion than is presented in the foregoing data. In 5 cases of the group amputation was performed subsequently; in 4 on account of continued drainage and nonunion, and in 1 case on account of nonunion, which might have been remedied by a bone graft. Seventeen patients died subsequently. All but 2 of the 17 died from extension of the tuberculosis. They lived an average of four and a half years. The operation relieves the patients of a painful, distressing condition and restores them practically to full activity.

The Roentgenologic Aspects of Primary Tumors of the Lungs.—HYDE and HOLMES (*Am. J. Roentgenol. and Rad. Therap.*, 1927, **18**, 235) claim that primary lung tumors are not as rare as is commonly believed. An attempt at earlier diagnosis should be made. An understanding of the underlying pathologic process in continuity is necessary to the interpretation of the Roentgen findings. A correlation of the clinical and roentgenologic findings is necessary for the diagnosis. Rarely the Roentgen findings present features which are practically pathognomonic. Among the more suggestive findings is that of a dense hilar mass with nodules and radiations extending into the lung field. The most common or typical lung tumor is carcinoma of the right bronchial tree in a male in the fifties, appearing in the Roentgen findings as a hilar shadow with radiations extending into a small immobile lung field, but which may be obscured by shadows of pneumonic or other complicating processes.

Cholesterosis of the Gall Bladder.—JUDD and MENTZER (*California and West. Med.*, 1927, **27**, 487) say that cholesterosis of the gall bladder is probably a localized manifestation of altered fat metabolism in the entire body. The cholesterosis was in the form of "strawberry," "fish scale," or papillomatous lesions. The clinical diagnosis of gall-bladder disease is correct in about 85 per cent of cases, but it is impossible to determine clinically the type of disease in as large a percentage and whether stones are present in about 35 per cent of cases of cholesterosis of the gall bladder. The Graham-Cole technique has more than doubled the roentgenoscopic accuracy of the diagnosis of diseases of the gall bladder, but negative films are not of decided value. Cholesterosis of the gall bladder with or without stones is a surgical problem provided pain is a dominant symptom. In 30 per cent of the 500 cases with stones the stones were single. In 99 per cent of all the cases complicated with gall stones in this series the stones were of the cholesterin-rich type. This lends support to the theory that cholesterosis of the gall bladder is primarily a metabolic disturbance. Twenty-six per cent of the gall bladders removed as a routine show cholesterosis. Inflammatory changes in the pancreas and liver are much less evident with cholesterosis of the gall bladder with and without stones than with other forms of gall bladder disease.

Internal Derangement of Knee Joint.—WALLACE and PERMAR (*J. Bone and Joint Surg.*, 1927, **9**, 667) reports that tender areas at site of pannus formation are signs of trouble within the joint. Lack of complete extension is the most important sign in internal derangement of the knee joint. Many patients have knee joints which have accommodated themselves to weakness and are in a position of slight locking all the time, as evidenced by lack of complete extension. A misplaced or hypertrophied semilunar cartilage or fat pad is a foreign body which acts as an irritant which will produce a vicious pathologic cycle leading to destruction of the joint. Careful and repeated examination is necessary in making a diagnosis of internal derangement of a knee joint. Removal of the offending object is the surest way to effect a cure.

PEDIATRICS

UNDER THE CHARGE OF

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Effects of Abundant Cereal Intake.—COWGILL, JONES, FRISCH and JACKSON (*J. Am. Med. Assn.*, 1927, **89**, 1770), in their feeding experiments, showed that when suitable adequate supplementary foods are employed, the use of whole-grain cereals and likewise one of the milled wheat breakfast foods, so as to furnish as much as 84 per cent of the calories of the diet was compatible with excellent growth, reproduction, lactation, and general physiologic well-being in the rat. A milled corn product such as hominy was only slightly, if at all, inferior to these products. The results of diets containing even as much as 93 per cent of whole-grain calories approximated those of current normal standards. It seems almost impossible to set the physiologic limits to the amounts of whole-grain cereals that may be included as a chief source of energy in an otherwise balanced diet of the rat. Success with the very large inclusion of cereals as sources of energy in the diet depends on the proper choice of the foods that are used to supplement the cereal. The authors confirmed the value of certain combinations of liver and lettuce in promoting growth as observed by Osborne and Mendel. Caution must be observed in applying results obtained from rat experiments to the nutrition of man. In the opinion of the authors, their results demonstrate conclusively that cereals may be used by man to a much greater extent than is common in this part of the world, and that high cereals in the diet will give successful nutrition if suitable supplemental foods are provided. Contrary to the usual opinion these supplements need not include milk.

Effects of Abundant Cereal Intake.—COWGILL, JONES, FRISCH and JACKSON (*J. Am. Med. Assn.*, 1927, **89**, 1930) state that diets consisting of whole-wheat cereals and other cereal products up to 65 per cent, and such easily obtainable food materials as whole-cooked egg, 20 per cent, cane molasses, 15 per cent, and a daily allowance of 15 gm. of fresh lettuce were sufficient to meet the nutritive demands of rapid growth in the white rat. Similar diets in which the cereal constituted 80 per cent of the mixture, whole-cooked egg, 12 per cent, and molasses 8 per cent, together with a daily allowance of 15 gm. of fresh lettuce promoted good to excellent growth, the limiting factor being apparently the amount of protein in the diet. Under these conditions corn meal did not yield as good results as oatmeal or whole wheat. The content of protein in the diet also seemed to bear some relation to the ability of such mixtures to meet the demands of lactation. Extreme diets containing whole-grain cereal 93 per cent, egg yolk, 3.5 per cent, and molasses, 3.5 per cent, together with a daily allowance of 15 gm. of fresh lettuce no longer met the demands for rapid growth. The

amount of protein in the ration seemed to be at least one limiting factor, being definitely inferior to oatmeal and wheat. It is possible to supplement whole-grain and other cereal products easily and satisfactorily for growth, reproduction and lactation with simple foods other than milk. These include egg, molasses and lettuce, providing the cereal does not represent more than 65 per cent of the mixture. At as high a level of intake as 80 per cent of cereal, the demands of growth may be met satisfactorily in similar fashion. Under these influences lactation may or may not be successful. When the same supplementary foods were used but making the whole-grain cereal constitute 93 per cent, egg yolk, 3.5 per cent, and molasses, 3.5 per cent of the mixture, together with a daily allowance of lettuce, satisfactory growth was obtained with oatmeal and wheat but not with corn meal.

Tetanus Anatoxin and Antitetanus Immunity in Mother and Newborn. —Nattan-Larrier, Ramon and Grasset (*Ann. de l'Inst. Past.*, 1927, **41**, 848) used rats and guinea pigs in their experimental work. They found that the specific immunity acquired by the female in gestation under the influence of injections of tetanus anatoxin is transmitted to the young. On the day of birth, the blood of the newborn animals contained tetanus antitoxin in a quantity equivalent to or slightly superior to that of the mother. This immunity is passive and is prolonged up to two months after birth. The very young rabbit may be actively immunized either by injection or by ingestion of tetanus antitoxin. Immunity obtained by subcutaneous injections of antitoxin is far superior to that obtained by the oral route, especially when the large quantities of antitoxin used in the latter method are considered. The addition of such products as tryparsamide or trypoxyl to the antitoxin dose does not injure antitetanus immunity. Immunity seems to be favored by these additions to a certain degree, but less than by the addition of tapioca. Immunity in the newborn infant is passive, due to the passage of the maternal antitoxin through the placenta. The infant subjected to injections of tetanus antitoxin is capable of developing a specific active immunity, which is weaker than that developed in adults with relatively smaller quantities of antitoxin.

Peribronchial Infiltration after Respiratory Infections in Childhood. —Heiman and Cohen (*Arch. Ped.*, 1927, **44**, 677) have observed an atypical, but frequent pulmonary complication. This syndrome consists of dullness on percussion, usually over both lower lobes, often in the axillary regions, low-grade fever over a long period ranging from 100° to 101°, and in most cases a cough. Râles, bronchial breathing, or changes in voice were not found. This picture was found as a complication of grippe or influenza, measles, pertussis, scarlet fever, or other upper respiratory infections. Although the course tends to be chronic, the involvement may be found early in the course of the primary infection. It then serves to prolong the high fever and toxemia of the initial infection. In the chronic stages the patient suffers little, for the fever is not high, but in some cases the cough is distressing. Recurrences are common because the focus of chronic infection in the lung sensitizes instead of immunizing the patient. The recognition of this syndrome is useful in accounting for the many coughs and fevers,

which have been unexplained in the past. A study of the pathogenesis and pathology of pneumonia leads the authors to believe that this pulmonary syndrome is a streptococcus pneumonia of the interstitial type, without alveolar exudation. Such a form of pneumonia is not uncommon in children. The interstitial lesions may completely resolve after a long time or become indurated, causing a permanent dullness of the region affected. Roentgen-ray studies have shown fine infiltration in about one-half of the cases studied, with accentuation of the lung markings in most of the others. The prognosis is excellent, as there were no deaths in this series and none of the children suffered from deterioration of general health. The treatment was fresh air, heliotherapy, and Roentgen ray therapy, in protracted stubborn cases opiates were given to relieve the cough.

Acute Disturbance of Lung Function in Pneumonia. Methods of Oxygen Treatment.—BARACH (*J. Am. Med. Assn.*, 1927, **89**, 1865) claims that the important consideration in pneumonia is the impairment of the lung function. This is primarily the interference with adequate oxygen diffusion through the lung with the consequent deprivation of oxygen in the tissues. He presents a group of cases in which the withdrawal of oxygen therapy during the course of the disease was followed by distressing and dangerous symptoms such as cyanosis, increased dyspnea and subjective discomfort, rising pulse and respiration. The existence of this type of response illustrates the need of oxygen for proper maintenance of the lung function in patients with marked cyanosis and dyspnea. The inhalation of from 40 to 50 per cent of oxygen in the desperately ill patient may prolong life, and in a certain percentage of cases may be a life-saving measure. In removing oxygen administration, it is advisable to do so, gradually watching the patient carefully for evidence of oxygen want. He administers it by nasal catheter in conjunction with a calibrated gauge. He also uses the oxygen tent in which the air is cooled and dried by passage over ice, and the oxygen chamber in which the ventilation is achieved by thermal circulation of the air.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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The Place of Erythema Nodosum in Medicine.—WALKER (*Brit. J. Dermat. and Syph.*, 1927, **39**, 241) reviews *in extenso* the recent literature dealing with erythema nodosum as a symptom of constitutional disease.

The first section of this paper is a critique of Stephen Mackenzie's paper, which gave to erythema nodosum its original rheumatic stamp. This possibility the author is inclined to minimize, pointing to a number of inaccuracies in Mackenzie's paper. He considers that there is a considerable body of evidence especially accumulated by Lendon and Harrison to the effect that erythema nodosum is in a certain proportion of cases an acute specific infectious disease deserving the title of nodal fever. Symes has recently taken the position that this acute specific fever strongly predisposes to tuberculosis. Osler pointed out the association with tonsillitis as suggestive of an acute infectious disease. Walker himself considers that half the clinical cases of erythema nodosum are classifiable as an acute, mildly specific, infectious disease with an incubation period of about fourteen days; a prodromal period which may be so intense as to simulate typhoid fever; a precise and uniform exanthem with frequent relapses and a precarious convalescence. The disease is more common in spring and autumn and appears up to early adult life, attacking women rather than men. Instances of the epidemiology of the disease are cited. The second possibility which is considered is that of an association between erythema nodosum and tuberculosis. This has been dealt with in the literature since 1907, including the reports of Hildebrandt, Landouzy, Zieler and Vetlesen. Landouzy reports successful inoculation of tuberculosis into a guinea pig from a node in a patient who also presented a tubercle bacillus in the coagulum of a vessel in another node. Zieler failed in 400 histologic sections to find any evidences of tuberculosis. Willan (1798) was the first to observe the clinical association. Uffelmann was the first to observe the more prolonged and indolent clinical course of the "tuberculous type." The contributions of American authors, including Abt and Foerster, are cited. The author then analyzes the group of nontuberculous, nonfebrile cases, including Duhring and Jansen's descriptions of specific luetic erythema nodosum; cases reported by Holland as associated with Streptococcus septicemia; Osler's observations on erythema nodosum in typhoid fever; Rosenow's work on a diphtheroid found in the nodes. The author concedes that there is a group of cases which do not fall into the previous classifications and which have a multiple etiology.

Treatment of Urticaria with Ephedrin.—KESTEN (*Arch. Dermat. and Syph.*, 1927, **16**, 189) reports on 6 patients with chronic urticaria treated with ephedrin sulphate orally, with complete relief in 2 and improvement in 2; of 11 patients with chronic urticaria and angioneurotic edema similarly treated, of whom 7 were cured, 2 improved and 2 remained unimproved. The dosage in these patients was notably high, the minimum being 50 mg. every two to six hours and the maximum as high as 120 mg. every two hours. Percutaneous tests were made with the grouped proteins and blood pressure taken both before and during treatment. There were no harmful effects. Symptoms occasionally complained of included tremor of the hands, weakness, headache, restlessness, palpitation, insomnia, drowsiness and nausea. Persistent rise of 5 to 30 mm. occurred in systolic pressure during the course of the treatment. No etiology could be identified in 4 of the 6 cases in a first series and in 3 of the 11 cases in a second series.

The duration of symptoms before treatment ranged from one week to thirteen years, the last-mentioned case being unimproved, although 1 with a six-year intermittent history was apparently cured. Two patients were sensitive to specific proteins. Constipation and focal infection seemed to have been conspicuous in the presumptive etiology. Symptoms seldom recurred after the drug was discontinued. A mild urticaria following as part of serum sickness was not relieved; papular urticaria, erythema multiforme and chronic eczema did not respond, although there was some diminution of the itching.

OBSTETRICS

UNDER THE CHARGE OF

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The Responsibility of the Obstetric Teacher in Relation to Maternal Mortality and Morbidity.—In this article WATSON (*Am. J. Obst. and Gynec.*, 1927, **14**, 277) brings out a very important topic on obstetric teaching regarding maternal mortality and morbidity. It emphasizes the importance of obstetric teaching and further shows that it is well nigh impossible to compare the death rate in childbirth of fifty years ago and of the present day, as registration was in the past much more defective than it is today. It takes up the question of the high mortality and puerperal sepsis and tabulates results in Scotland from 1855 to 1922, as it is usually agreed that figures and statistics are fallacious, but some of the data given reveals that there has been a very considerable reduction in the death rate from sepsis and other causes in the last seventy years. Maternal mortality in countries in which registration of deaths is on a comparable basis, such as Scotland and the United States, we find there is little difference, that the maternal mortality from all causes in all countries varies from 4 to 7 per 1000, and has changed little in the last twenty years. Campbell, of England, is quoted as giving the maternal death rate reduced one-third, the infant mortality rate as being halved since the beginning of the century, yet this mortality rate is little lower than it was twenty years ago. The author questions whether some of these deaths are preventable, and we have reached a reducible minimum in the pregnant and parturient woman. The idea of obstetrics being a surgical specialty and the obstetrician first and foremost a surgeon is discussed and gives a great deal of credit to the foregoing fact resulting in the improvement in technique in delivery and operating rooms and points out clearly that with surgical procedure in mind the young practitioner comes

to believe that every case must be subject to surgical procedure. An effort on the part of the teachers to impress upon their pupils the essential normality of the vast majority of cases and the dangers of unnecessary interference. He points out the great need of medical midwifery, he considers that the student in hospital training sees too many instrumental deliveries in proportion with the normal cases. There are several reasons given for the unnecessary interference. Among these are the prompt and efficient technique of the set-up for operative delivery; further, that when the pupil sees the skilled obstetrician emerge successfully from a difficult forceps, version and breech delivery that there is the thought imparted to the pupil that he likewise can as successfully accomplish this result. He urges that students should never be allowed to leave the case with the wrong impression and that the instructor must take great pains to impress upon his pupils the indications for the interference and the fact that years of experience and study are necessary before he too can bring to a successful conclusion many of the complicated cases. He emphasizes the student's course and clinical instructions, stress being laid on diagnosis, prenatal pelvimetry and abdominal palpation, the types of pelvis, presentation and position and the estimated relative size of the head and the pelvic brim; the improvement in the treatment of various complications of pregnancy; the early and late toxemias, the heart affections, full physical examination, the blood pressure and urine examinations throughout the entire antenatal state. He quotes the late Dr. Studdiford, who found that over a period of seven years in the Sloane Maternity Hospital in New York, 20 per cent of the patients required special advice and treatment and that 12 per cent were admitted to prenatal wards. The whole article is filled with excellent advice and guidance for those who are teaching obstetrics and who are engaged in the active practice of obstetrics and midwifery, all this to one end: That maternity cases can be better cared for in hospital surroundings. To help and maintain a high standard of obstetrics and to gain a higher level for this most important branch of medicine and surgery.

GYNECOLOGY

UNDER THE CHARGE OF

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Viability of Cast-off Menstrual Endometrium.—The question of the viability of the epithelium found in the menstrual fluid has been of intense interest since Sampson suggested his theory of endometrial transplantation. It has been held by some investigators that the

endometrium of the menstruating uterus is less viable than at any other time during the menstrual cycle and that the epithelium found in the menstrual fluid is actually nonviable. In order to prove or disprove this premise, CRON and GEY (*Am. J. Obst. and Gynec.*, 1927, **13**, 645) cultured epithelium from a menstruating uterus. The epithelium was obtained by gently removing with a dull curette a small amount of the menstrual flow during the second day of the menstrual period. This material was put in a plasmatic medium containing heterologous embryonic extract as the growth-promoting substance. Signs of cellular activity occurred a few hours after incubation. This consisted of a very dense and massive emigration of leukocytes, which rapidly spread far into the medium over a period of several days. The fixed tissue cells began to emigrate on the second day, when radial overgrowths of spindle-shaped cells and sheetlike outgrowths of epithelial cells appeared at the periphery of the tissue fragments. The more active fragments were transferred every four or five days for over a month. They believe that the above experiment establishes beyond any doubt that the epithelium of the decidua menstrualis, which is found in the menstrual fluid, is viable. This fact, of course, greatly supports the theory of Sampson.

Papillary Cystadenoma of the Ovary.—It is very difficult for those of us who are called upon to remove a papillary cystadenoma of the ovary to give a definite prognosis. These tumors are usually considered benign with malignant possibilities, but just which ones will become malignant is the question that is frequently impossible to answer with any degree of accuracy. MAYFIELD (*Northwest Med.*, 1927, **26**, 236) has investigated the records of a series of 100 cases of this disease which were observed in the Mayo Clinic. He found that papillary cystadenoma varies in frequency from 16 to 18 per cent of all ovarian cysts. They are most probably developed, he believes, from epithelial structures derived from the germinal epithelium. Bilateral tumors are frequent, having been found in 43 per cent of the cases. He states that Roentgen ray and radium treatment should be given in addition to the operative procedure in every case in which implantation or metastasis is found. Even when it is not apparent that the tumor capsule is perforated recurrence may take place from unrecognized implants or metastases. Disregarding the degree of malignancy present, 44 per cent of the patients lived without recurrence of symptoms for an average period of seven years and seven months, and 35 per cent of the patients died from recurrence within an average period of two years and two months after operation. The prognosis depends on whether the tumor capsule is perforated, the histologic evidence of malignancy of the tumor and the extent of the involvement of the surrounding tissues. The following figures are based on an interval of seven years and seven months after operation: If the capsule is perforated and the malignancy of the tumor is of low grade a 15 per cent chance of recurrence exists. If the capsule of the tumor is perforated and the malignancy is of high grade a 57.9 per cent chance of recurrence exists. In 10 per cent of the cases in the group with perforation of the capsule and tumors of a low grade of malignancy, death is caused by recurrence; in 75 per cent the patient survives without recurrence. In the group in which

a tumor of a high grade of malignancy has perforated 50 per cent of the patients die from recurrence and 15.8 per cent live without recurrence. While the symptoms are variable and inconstant, there are in many cases certain points of similarity in the localization of the pain in the lower abdomen or pelvis, in its bearing down character, its moderate severity and in the sensation of weight or fullness in the pelvis. This type of pain with a history of pelvic discomfort, menstrual irregularity, indefinite vesical or gastrointestinal symptoms, together with the presence of a rounded, firm, cystic tumor in the pelvis or abdomen is suggestive but not definite evidence of a papillary cystadenoma of the ovary. In 52.5 per cent of the cases investigated before the menopause there was some type of menstrual irregularity. Ascites was present in 31 per cent of the cases and usually indicated an advanced stage with perforation of the tumor capsule and peritoneal implants. The preoperative diagnosis is always uncertain and the tumor is frequently mistaken for uterine fibromyoma.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Paroxysmal Spasm of the Eyelids as a Postencephalitic Manifestation.—ALPERS and PATTEN (*Arch. Neurol. and Psychiat.*, 1927, **18**, 427) regard as postencephalitic the blepharospasm that occurred in a young man, aged thirty-four years, who had suffered from pain about the head and extremities for six months. On the appearance of the pain in the arms the patient noticed that he felt drowsy and dropped off to sleep in the daytime. The drowsiness lasted only one month and disappeared without further signs. Later he noticed drooping of both eyelids, which gradually progressed and persisted. He denied diplopia at any time. Simultaneously with the appearance of the drooping of the lids was the occurrence of stammering, salivation and increasing rigidity. In addition, he became troubled at this time with a spasm of the eyelids. They would suddenly go into spasm, closing completely and remaining so for several minutes unless he pried them open with his fingers. These contractions were painful and increased in severity together with general stiffness. The laboratory examination, including a Wassermann reaction, was practically negative. From a review of other cases as well as their own, the authors state that the condition is comparatively rare and in every case it has been a late sequela of encephalitis, occurring at varying intervals after the acute attack. In this case it occurred three years after the acute illness, simultaneously with the development of a Parkinsonian state. Others have reported it from seven months to four years after the onset of the encephalitis. Nothing seems to relieve the attack. The lesion is probably located in the subthalamic region.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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Ephedrin and Cocain Synergy.—It is recognized that the action of cocain and epinephrin on the blood pressure is synergistic and that this correlated action includes toxicity. It has been shown that ephedrin possesses most of the properties of epinephrin in that it stimulates the sympathetic nervous system, differing, however, in maintaining an increased blood pressure for a longer period of time. Moreover, it has been demonstrated that there is a synergistic action between ephedrin and epinephrin, insofar as the action on the blood pressure is concerned. Therefore, if ephedrin produces changes identical with those produced by epinephrin, its action on the blood pressure and toxicity should be synergistic with cocain. Inasmuch as he was unable to find any investigations which had been done on this phase of the subject, Ross (*Arch. Otolaryngol.*, 1927, **5**, 509) conducted several experiments on dogs. The first group of dogs was given cocain (0.5 per cent solution) *via* the femoral vein to determine the minimal lethal dose. The second group of animals received 0.1 per cent solution of ephedrin chlorid for a period of about twenty minutes. An interval of from thirteen to seventeen minutes was allowed to pass before the injection of 0.5 per cent cocain hydrochlorid and 0.1 per cent ephedrin hydrochlorid was begun. A third group was given similarly, cocain and ephedrin until dead. A final group of animals—cats—was inoculated intraperitoneally with varying strengths of cocain and ephedrin solutions. In the first group, the average minimal lethal dose of cocain hydrochlorid was 0.0153 gm. per kilogram of body weight. The average rise in blood pressure was 14 mm. of mercury. The average rise in blood pressure produced by ephedrin alone was 47 mm.; that due to ephedrin and cocain was 9 mm. The toxic dose of cocain was increased by the rise of ephedrin in cats that had not been anesthetized. From the results of his experiments the author concludes that ephedrin and cocain do not act synergistically on the blood pressure like epinephrin and cocain; and ephedrin does not increase, but decreases the toxicity of cocain.

Tinnitus Aurium.—Tinnitus aurium is such a dread affliction, and the treatment of it so disappointing, that any method which has been attended with however small a degree of success is worthy of record. Consequently, STURM (*J. Laryngol. and Otol.*, 1927, **42**, 449) cites several examples where relief from tinnitus has followed instillation of atropin into the middle ear through a previous perforation of the drumhead, or *via* the Eustachian tube, or by soakage of the intact tympanic membrane. The 2 cases where severe tinnitus of long-standing disappeared immediately following the local use of atropin had

middle-ear suppuration with large perforations. In the presence of paracutic deafness, shortened bone conduction, or any stage or degree of primary or secondary otosclerosis or nerve deafness, atropin has sometimes no effect, sometimes changes the pitch but not the severity of the tinnitus, often relieves, but has never cured. The author enters into a comprehensive discussion of the anatomic, physiologic and neurologic phases of his subject.

RADIOLOGY

UNDER THE CHARGE OF

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Effect of Roentgen Rays on Tuberculosis in Guinea Pigs.—FORD (*Radiology*, 1927, **9**, 235) inoculated 52 guinea pigs intraperitoneally with a virulent strain of tubercle bacilli and subjected half the group to Roentgen irradiation, the remainder being used as controls. She found that with a dosage of Roentgen rays comparable to that used in the treatment of human beings the development of tuberculosis in the guinea pigs was not retarded. The fact, however, that guinea pigs are unusually susceptible to tuberculosis, that the treatment of small animals is necessarily applied to the entire body, which undoubtedly affects the therapeutic result, and that the bacilli were overwhelmingly virulent, prevents the data here presented from being conclusive evidence that Roentgen rays are without influence on generalized tuberculous infection.

Roentgen Ray Treatment of Hypertrophied Prostate.—The first attempt at Roentgen therapy of prostatic hypertrophy was made by Robarts, of St. Louis, in 1902. Others have tried it since then with excellent results. YOCUM (*Arch. Phys. Ther., Roent. Ray, Rad.*, 1927, **8**, 416) points out that the average case is a poor surgical risk and mortality from operation is high, whereas Roentgen therapy is simple and safe and should be tried before attempting surgical intervention. He employs filtered Roentgen rays of high voltage. The retention is relieved, the frequent and painful urination is lessened and the gland is reduced by one-third on an average. The best results are obtained in patients past fifty-five years of age. The older the patient and the greater the surgical risk, the better the result from Roentgen therapy.

Roentgen Ray Treatment of Bronchial Asthma.—GERBER (*Radiology* 1927, **9**, 192) feels that Roentgen therapy has a definite place in the treatment of true bronchial asthma and in whooping cough. Some of

the cases of bronchial asthma which he has treated did not have any further paroxysms for two years after a single course of treatment. In many others there was benefit which could be maintained by judicious repetition of treatment in smaller doses. Approximately 25 per cent of the cases of bronchial asthma obtained no relief, and this percentage applies also to cases of whooping cough. For bronchial asthma Gerber employs two large portals of entry, front and back, over the mediastinum. Over each area 15 to 20 per cent of a skin-erythema dose is applied, with short-wave lengths at 50 cm. distance. If no beneficial effect is obtained, the spleen is irradiated. Courses are repeated, if necessary, in three to six weeks. For whooping cough a smaller dose, 7 or 8 per cent of an erythema dose, repeating on alternate days until a maximum of five treatments has been given.

NEUROLOGY AND PSYCHIATRY

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On Palilalia.—CRITCHLEY (*J. Neurol. and Psychopath.*, 1927, **8**, 23) reports 7 cases, 4 associated with postencephalitic syndromes and 3 associated with cerebral arteriopathies. The author states that there should be no real difficulty in diagnosing palilalia if the essential features, self-repetition, acceleration of speech and increasing inaudibility are kept in mind. He discusses its differential diagnosis. He notes the following important clinical findings: Palilalia disappears during performed speech automatisms, as reading aloud, singing or reciting. It may occur not only during intellectual speech but also in emotional, interjectional speech or it may be absent from the latter. It may be constant in appearance but frequently varies in intensity with the physical condition of the patient. The number of repetitions varies with individual cases and with the length of phrase repeated. Where the speech comprises two or more sentences usually it is the last sentence alone which is repeated. No case has been recorded associated with evidence of paligraphia or palikinesia. In a few cases there has been a hint of echolalia and very rarely echopraxia. There is no aphasia in the accepted sense of the word. Emotivity and intellectual impairment may be present and there may be various physical accompaniments. Cases have been reported in pseudo-bulbars, in post-encaphalitics, in Alzheimer's disease and in the idiopathic variety of paralysis agitans. The anatomical basis of the disorder has not been established. There is some dispute as to the mechanism of the disorder. It has been considered as related to verbal stereotypy, stammering and spasmodic laughter and crying. The author would

bring it into relationship with the exaggeration of the more automatic activities which may be seen in some cases of postencephalitic Parkinsonism and pseudobulbar palsy together with the delay in checking the movement at will. He brings his view into line with that of Claude whom the author quotes as describing a somewhat allied speech phenomenon "verbal antepulsion and festination."

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Hyalin Degenerations of the Islands of Langerhans in Nondiabetics.—WRIGHT (*Am. J. Path.*, 1927, **3**, 461) reports 5 cases in 84 routine autopsies, where hyalin degeneration of the islands of Langerhans was found on histologic examination, but in which, during the lifetime of the individuals, there was no clinical evidence of diabetes mellitus. The cases ranged in age from fifty-three to sixty-nine years. Careful attempts were made by means of various stains to determine the source of the hyalin, in contrast to the hyalin degeneration described by Opie, in diabetes mellitus, where the hyalin is thought to result from the epithelial degeneration of parenchymatous cells; this appears morphologically to be the end result of a slow change occurring in the fibrous tissue surrounding the capillaries of the islands. The character of the lesion suggests a toxic origin, the injurious agent acting slowly and progressively over a prolonged period of time. The degenerative process in each case affected less than one-third of the islet tissue observed, in striking contrast to Opie's observations where the degenerated islands outnumbered the normal ones. A moderate amount of hypertrophy of unaffected islands was observed in 3 cases, but this bore no constant relation to the amount of islet tissue involved in the degenerative process. No cases were observed in which the islet tissue was completely replaced by hyalin. Regeneration of islet cells does take place, but the regenerative power of the cells is gradually worn down and finally when sufficient islet tissue is destroyed the phenomena of diabetes mellitus appear. These cases may, therefore, be placed in the prediabetic group, sufficient insular tissue being normal to carry on the functions of carbohydrate metabolism.

Gastroscopic Removal of Radium Capsules.—CLERF (*Am. J. Roent. and Rad. Therap.*, 1927, **17**, 635) reports the case of a boy, aged thirteen years, who swallowed two capsules containing radium element which had been placed in a rubber bag and applied to the posterior nasal chamber for the treatment of sarcoma. A Roentgen ray examination localized the object in the stomach. An 8-mm. gastroscope was passed into the stomach and with the aid of a double-planed roentgenoscope the bag was grasped with forceps and removed.

HYGIENE AND PUBLIC HEALTH

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Review of Literature on the Physiologic Effects of Abnormal Temperatures and Humidities.—SAYRES and DAVENPORT (*U. S. Pub. Health Rep.*, 1927, **42**, 933) summarize their review as follows: 1. Temperature and humidity, according to the literature, are the two most important atmospheric conditions that affect the health and efficiency of people in their living and working places.

2. The belief that the ill effects experienced from exposure to crowded conditions in enclosed spaces were generally due to gaseous constituents of the air has been proved false by experiments conducted by numerous investigators. It then was thought that perhaps there were organic poisonous substances exhaled by people; this also has been proved by experimentation to be erroneous and the part played by high temperature and humidity was finally recognized.

3. Abnormal temperatures and humidities are encountered through seasonal changes in the Temperate Zones and with changing elevations in tropical climates. The large degree of conformity in the mortality curve of the cities and states throughout the world during different periods of time seem clearly to prove that there is some definite relation of weather to disease. The effects of high temperatures encountered in seasonal variation in the Temperate Zones are considered acute, many sudden deaths occurring during certain periods of excessively hot weather, while the effects of exposure to a tropical climate are more chronic.

4. The literature in regard to the action of cold on animals is very meager. Extreme cold seems to be borne better by the human organism than extreme heat; this is partly due to the fact that the effects of cold can be mitigated by artificial control. Explorers in Antarctic regions found that in still weather no temperature was low enough to prevent outdoor work, but that it was impossible to exist outside for any length of time at very low temperatures when the wind was blowing.

5. In regard to the relation of sex and age to susceptibility to abnormal atmospheric conditions, women appear to react more readily than men, and children and old persons are more easily affected. Men between thirty and forty years are said to be best adapted to endure the rigors of Arctic exploration.

6. A few of the large number of occupations which require exposure to extreme heat, humidity and variations in temperature are listed.

7. The source or cause of animal heat was an unsolved mystery to the ancients. They had no thermometers and their knowledge of

the constant heat of the human body was imperfect. A scientific attitude toward the subject was developed through contributions from time to time of knowledge obtained by various investigators, who finally determined that animal heat is the result of processes of combustion within the body.

8. It has been determined by observation that there is a limit to the heat-regulating power of the body and that an animal cannot live indefinitely in a temperature higher than that of its body; according to Bernard, the larger the mass of the animal the quicker the death. Remaining at rest in saturated air at 91.5° F. for one hour with no air movement caused an increase in body temperature.

9. The effects on the human body of abnormal air temperatures are modified by humidity, air motion, exercise, physical condition of persons exposed, food eaten, clothing worn and individual idiosyncrasy: (*a*) Humidity increases the discomfort and ill effects of both high and low temperature. Comfort, as determined by both sense and physiological reactions, depends solely upon effective temperature. At 32° the effective-temperature line coincides with the dry-bulb temperature line; hence, in this particular case, dry-bulb temperature is the only factor in determining comfort. In the comfort zone comfort depends equally upon wet-bulb and dry-bulb temperatures. At about 132° the effective temperature coincides with the wet-bulb temperature, and for this case the wet-bulb temperature is the only factor. Below 32° the effect of humidity is reversed—that is, the lower the humidity the greater the feeling of warmth. (*b*) The limiting physiologic reaction caused by high temperatures, as determined by comfort, is not body temperature but the pulse rate. When this is above 135° the first symptoms of discomfort arise; when above 160° the effects are severe to distressing. (*c*) Air movement decreases the discomfort of high temperatures below 98° F.; moving saturated air above 98° F. was found to be of no benefit and, apparently, is even disadvantageous. A thermometric chart is given showing effective temperatures for different air velocities at different temperatures and humidities, as well as for still air conditions. (*d*) The upper limit in atmospheric conditions at which work can be performed efficiently corresponds to a dry-bulb temperature of 100° and a relative humidity of 30 per cent, or 90° to 95° F. in still saturated air, even when stripped to the waist. The optimum temperature at rest is around 66° F.; and with hard work the optimum temperature is 59.5°; 43° F. was pronounced as too cold with or without air movement, regardless of humidity. In still air no temperature is too low to prevent outdoor work. (*e*) Normal clothing at ordinary humidity was found to have the cooling effect of wind as compared with that obtained with the subject stripped to the waist. On the other hand, clothing under certain conditions is advantageous in increasing loss of heat by evaporation and decreasing heat gain by radiation and convection; in fact, man is capable of increasing evaporation materially by suitable clothing. At rest in still air with a temperature of 65° to 70°, and with 100 per cent relative humidity, subjects stripped to the waist felt from "slightly cool" to "comfortable;" under these same conditions with moderately hard work they felt "comfortable." At rest in still air, with temperatures from 55° to 60°, 100 per cent relative humidity, clothing was required for comfort, while at moderately hard work under these conditions the subjects were "com-

fortable" to "cool" stripped to the waist, and at 45° to 50° subjects working moderately hard felt "cool" stripped to the waist.

10. Death generally takes place when the body temperature is raised to between 109° and 113° F., although no direct statement was found in the literature as to the air conditions and the length of exposure required to raise the body temperature to the fatal point. The lowest body temperature compatible with life is said to be 78.8° F., although Lefèvre found that a rabbit died when the temperature of the rectum had fallen to between 60° and 65° F.

11. According to one observer, the minimum accident frequency in factory work in both men and women was at 65° and 69° F. At lower air temperatures it gradually increased to a similar extent in men and women until at 50° to 54° it was 35 per cent greater than at 65° to 69°. At temperatures below 49° the frequency fell off slightly. This fall may have been due to the workers being too cold to keep up their usual rate of production. In such a case they would expose themselves to less risk by accident. At temperatures above 65° to 69° the accident frequency showed only a slight rise in the women, but in the men it increased rapidly, and at temperatures above 75° it was 39 per cent greater than at 65° to 69°. Probably this difference was due to the fact that the work of the men was often of a heavier character than that of the women, and the greater the exertion required, the more trying must be the effect of exposure to high temperatures. During the sixteen months preceding the installation of the cooling plant in the Morro Velho mine there were 20 fatal accidents, while during the sixteen months' period following the installation there were only 6 fatal accidents.

12. It has been found that a moderate increase of temperature—within physiologic limits—augments the action of drugs and toxic substances, such as carbon monoxid, mustard gas and lead.

13. A list of the symptoms—subjective and objective—observed by different investigators is given. The most commonly observed subjective symptoms were cramp, headache, pain in the back, dizziness great thirst, chilliness although the body temperature might be high, diarrhea, restlessness and insomnia. Chronic exposure to excessive heat results in lowered physical efficiency and diminished resistance to fatigue and disease. The principal objective symptoms noted were changes in body temperature, pulse rate and blood pressure, increased respiration and body metabolism, and loss of weight. The statement is made by one group of investigators that the pulse rate is probably the best single physiologic measure of discomfort due to high temperature.

14. The action of high temperatures on muscular tissue is discussed, especially as a cause of fatigue.

15. The effect of cold on the body temperature up to the point of freezing is given as described in Lefèvre's "law of refrigeration."

16. Measures for the prevention of ill effects of exposure to high temperatures are given under personal hygiene and ventilation and refrigeration of working and living places. The economic value of the proper ventilation and cooling of working places is discussed. Measures of personal hygiene to combat high temperature are: Suitable clothing, breaks in tropical life by visits to the temperate zone and discretion in the use of food and drink.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 19, 1927.

The Alkaline Decomposition of Cystin.—J. C. ANDREWS (from the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania, Philadelphia). The results here reported were obtained by treating cystin with sodium hydroxid, both at boiling and at room temperatures and both with and without the presence of Pb^{++}. At room temperatures the slower reaction made it possible to follow more accurately changes in the concentration of cystin, cystein, sulfid, and ammonia and in the rotation of the solution.

Among the results so far obtained are the following: Qualitatively speaking, the effect of the alkali is to cause gradual decomposition of the cystin with formation of sulfid from a part of the sulfur of the decomposed portion. In presence of Pb^{++} this sulfid is precipitated as lead sulfid. In absence of Pb^{++} it accumulates and soon causes reduction of some of the undecomposed cystin to cystein. The free sulfur resulting from this reaction reacts with more of the unoxidized sulfid to form polysulfid, which accounts in part for the yellow color of such solutions. The alkali racemizes the cystin more rapidly than it decomposes it.

The presence of oxygen causes a decided drop in the yield of lead sulfid obtained but the effect is too great to be accounted for entirely by atmospheric oxidation of the sulfid ion. Furthermore, to obtain maximum yields of lead sulfid it is necessary to have the plumbite present during the whole time of alkali decomposition. If the solution stands some hours or days before addition of the lead, the yield of lead sulfid is only about 25 to 50 per cent of that obtained when it is present during the whole period.

To obtain some measure of the concentration of sulfid in the solutions which contained an excess of Pb^{++}, electrometric determinations of the concentration of lead ion in various concentrations of alkali were made. The values ranged from 10^{-14} to 10^{-15} moles Pb^{++} per liter. Assuming the usual value for the solubility product of lead sulfid to apply here, we have 10^{-13} to 10^{-14} moles S^{-} per liter as the maximum concentration possible.

The formation of sulfid in the absence of Pb^{++} differs from the other reactions concerned in being highly influenced by the concentration of alkali. In all cases the sulfid concentration rises to a maximum and then falls. This maximum is about at the same level of concentration for both 1.0 M. and 4.0 M. NaOH but it is reached in less than half the time in the latter case. No other of these reactions shows a speed so directly influenced by the concentration of the alkali.

The formation of cystein is not alone the result of reduction of cystin by sulfid ion since for the first week or ten days of the reaction the

curves for cystein formation in the presence and absence of lead are practically identical. However, in the presence of lead, the cystin has by this time disappeared altogether and the cystein, which has reached its maximum value, gradually decomposes and reaches, in 4.0 M. alkali, practically zero in about eighty days at room temperature. Lower concentrations of alkali make these reactions somewhat slower but the effect is much less marked than in the case of sulfid formation. In absence of Pb^{++} the cystein reaches a much higher maximum before dropping and the drop is much more gradual.

The formation of ammonia is of general interest because of its bearing on the mechanism of amino-acid deaminization in the body. Some years ago van Slyke noted that the amount of ammonia derived from boiling a sample of cystin in alkali was multiplied several times over (18 per cent *vs.* 60 per cent) if the boiling was carried on in a copper instead of a glass container. In the present experiments the rather remarkable result was obtained that the production of ammonia is *inversely* proportional to the concentration of alkali from 4.0 M. NaOH to 1.0 M. NaOH. From 1.0 to 0.01 M. the ammonia production drops again.

In the presence of an amount of lead equivalent to the sulfur present the rate of ammonia evolution is more than tripled. This effect is not the result of catalysis by the lead sulfid formed. Addition of freshly precipitated lead sulfid to the solution had no effect on the production of ammonia. Moreover, the action is probably not catalytic in nature at all since reduction of the lead to 10 per cent of the theoretical gives a result only slightly higher than that obtained when no lead is present while doubling the theoretical amount of lead raises the percentage decomposition to 74 per cent as opposed to 18 per cent without any lead.

The figures obtained with copper show a much less marked effect from copper sulfate and no effect at all from the presence of metallic copper in the flask.

Trichomonas in Tissue Cultures.—M. J. Hogue (from the Department of Anatomy, Medical School, University of Pennsylvania). Trichomonas is a protozoan flagellate found in the alimentary canal and in the urinogenital system of man and of some other vertebrates. There is a question as to whether it is pathogenic. Some authors think it is injurious to the cells of the host, others that it affects the nervous system in some way. In this work the following species of Trichomonas and Pentatrichomonas were used: T. buccalis, T. hominis, T. vaginalis, T. gallinarum, T. muris, Pentatrichomonas ardin delteili. They were cultured and then introduced into the tissue cultures by means of a Barber pipette. Small pieces of the heart, the stomach and the intestine of chick embryos, seven and eight days old, were grown in Locke-Lewis medium and beautiful growths of fibroblasts, epithelial cells and sympathetic nerves were obtained. The Trichomonas moved about among the living tissue cells which were attached to the cover glass. One would occasionally attach itself to a fibroblast by inserting its axostyle into the cell and then whirl about on the axostyle. Sometimes they crawled along the edge of the fibroblast with their undulating membranes. In neither case did they injure the fibroblasts. Again they

were seen to crawl along the edge of a plate of epithelial cells which are very sensitive and easily contract, but the Trichomonas in no way disturbed these cells.

When a Trichomonas got into a plexus of sympathetic nerves it would wander freely about among the fibers, crawling along them by means of its undulating membrane and pulling itself up onto other fibers with its flagella. The nerves bent but did not break and after the Trichomonas had moved on they appeared normal. Apparently these species of Trichomonas do not exert any mechanical effect on the cells and nerve fibers grown in tissue cultures.

The Loss of Purkinje Cells with Advancing Age.—T. INUKAI (from the Wistar Institute of Anatomy and Biology, University of Pennsylvania, Philadelphia). Using proportional fractions from human cerebella, Ellis, in 1920, found the number of Purkinje cells to decrease from seventeen to eighty-five years in both sexes. The amount of loss was some 30 per cent. This observation on man raised the question whether a similar loss was occurring in other mammals. To test this the cerebellum of the albino rat was studied at different ages. Three males and three females were examined. The individuals in each pair were of like age but the pairs of different ages. As the two sexes were found to show the same loss the results may be presented in terms of the males only.

The cerebella were sectioned sagittally and on the average there were 840 sections for each cerebellum. Taking every third section Purkinje cells, both normal and pathologic, were counted in one-third of these sections. The number found was multiplied by 3 to obtain the total. Thus at two hundred days 540000 cells were found and at succeeding ages 87 per cent and 82 per cent of this number, respectively. In man, at the equivalent ages, the corresponding percentages were 88 per cent and 76 per cent. It appears, therefore, that in the male albino rat Purkinje cells are lost with advancing age in much the same way as in man. We should, therefore, expect the higher mammals as a group to behave in a like manner. Determinations were also made of the area of the cortex and the distribution of the cells throughout the cerebellum. It appeared from these determinations that the total number of cells in a given cerebellum is proportional to the area of the cortex. It was further determined that the loss of cells was evenly distributed on both sides and in all divisions of the cerebellum. There was no localization. Ellis had reported a greater loss in the right as compared with the left hemisphere. Handedness is, of course, more marked in man than in a quadruped so we have no comment to make on this difference in the records.

A study of the size of the Purkinje cells showed them to diminish from the vermis toward the hemispheres and to be smallest in the paraflocculus. As the percentages show, nearly 100,000 cells have been lost from the cerebellum of the oldest rat. Cells on their way to destruction are present at all ages and these pathologic elements are studied. In the oldest rat their number is very large, showing that this animal was destined to lose still more cells had it survived longer.

Two questions naturally arise: First, why does this loss occur?

Second, what effect does it produce? Without going into detail we have the impression that such a loss depends on intrinsic conditions rather than on those that are extrinsic and that perhaps it is related to the relatively late maturing of the cerebellum. In considering the effect produced it must be recognized that the remainder of the brain is also shrinking with advancing age and most probably, in part, through a loss of cells. However, as the cerebellum presides over the motor responses, imperfectly made both in the old rat and the old man, it seems possible that damage to the Purkinje cells contributes largely to defective performance.

There is one suggestive instance. It is industrial usage to prefer very young men for lofters, bridge builders, etc., where the work demands perfect muscular control, especially in relation to equilibration and it seems possible, therefore, that this industrial selection is related to the loss of these cells, as found in man.

A Comparison of pH Determinations by the Hydrogen Electrode and Colorimetric Methods.—C. G. JOHNSTON (from the Department of Physiological Chemistry, University of Pennsylvania). The wide application of studies of the hydrogen-ion concentration of blood and other body fluids suggests the importance of a simple method for these determinations. The hydrogen electrode method is generally taken as a standard but this requires skill, a considerable amount of time, and of blood. To overcome these disadvantages, colorimetric methods have been devised, based on the comparison of colors given by an indicator when added to an unknown solution and to buffer standards. Errors are encountered because the color of the indicator is influenced by proteins and salts as well as the pH of the solutions. Cullen[1] diluted the serum 20 times with physiologic salt solution and felt that the differences between the colorimetric and hydrogen electrode results were sufficiently constant to employ a correction to convert the colorimetric readings at 20° to the electrometric values at 38°. Hastings and Sendroy[2] reported that the correction was eliminated when they compared colorimetric readings at 38° with the electrometric at 38°. Bennett[3] and Austin, Stadie and Robinson[4] have compared the Cullen and the Hastings methods with the electrometric and gasometric methods and found the corrections to vary. The widespread use of the colorimetric methods makes these observations of great importance.

Another colorimetric method studied, originated by Levy, Rowntree and Marriott[5] and improved by Dale and Evans,[6] employs dialysis of the blood against physiological saline. Evans (1920–1921) found that this method gave results—on human blood and bicarbonate solution—0.20 pH higher than the electrometric. He at first suggested that the electrometric readings were at fault and should be corrected to correspond to the colorimetric.

[1] Cullen, G. E.: J. Biol. Chem., 1922, **52**, 501.
[2] Hastings, A. B. and Sendroy, J., Jr.: J. Biol. Chem., 1924, **61**, 695.
[3] Bennett, M.: J. Biol. Chem., 1926, **69**, 697.
[4] Austin, J. H., Stadie, W. C. and Robinson, H. W.: J. Biol. Chem., 1925, **66**, 505.
[5] Levy, R. L., Rowntree, L. G. and Marriott, W. M.: Arch. Int. Med., 1915, **16**, 389.
[6] Dale, H. H. and Evans, C. L.: J. Physiol., 1920–1921, **54**, 167.

The data in this report were obtained from dogs' blood. Dogs were bled 3 to 4 per cent of their body weight and the pH determined by the electrometric, dialysis, Cullen, and Hastings methods on samples taken before and after the hemorrhage.

The technique employed for the dialysis method was as follows: Blood was drawn from the femoral artery under oil, and oxalated. It was then transferred to a collodion bag suspended in 0.9 per cent sodium chlorid solution which had been brought to about pH 7.4 by removal of the CO_2 dissolved in the water. The salt solution as well as the blood was kept constantly under oil and stirring was minimized. After dialyzing for thirty minutes the sack containing the blood was removed leaving the clear dialysate to which 0.1 cc. of a 0.02 per cent cresol red solution was added. This was then compared with phosphate buffers 0.05 pH apart containing the same quantity of indicator. In a large series of determinations the variations in the corrections for the colorimetric methods investigated were as follows:

Method.	Readings at	Maximum variations of correction.
Cullen	20°	0.17 to −0.50 pH
Hastings	38°	0.00 to −0.18 pH
Dialysis	20°	−0.13 to −0.41 pH
Dialysis	38°	+0.02 to −0.15 pH

None of the colorimetric methods studied yields pH values which show a constant variation from the pH of blood as determined by the hydrogen electrode, so that no constant correction can be applied. Therefore neither the Cullen, the Hastings, nor the dialysis method can be used for the determination of the pH of blood where accurate data are required, even for comparative results.

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